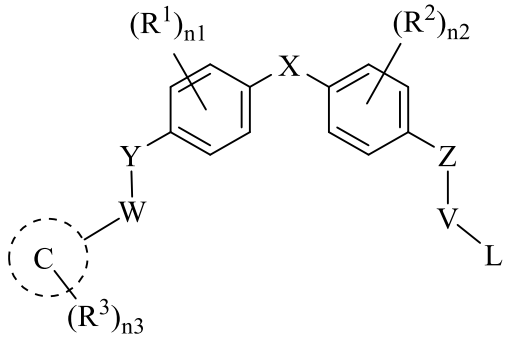
et al Molecular and Cellular Endocrinology **2012**, *352*, 70-78; van der Steen T. *et al International Journal of Molecular Sciences* **2013**, *14*, 14833-14859); and expression of AR splice variants (AR-Vs) which lack the ligand-binding domain (LBD) (Karantanos, T. *et al Oncogene* **2013**, *32*, 5501-5511; Andersen R. J. et al Cancer Cell 2010, 17, 535-546; Myung J. K. *et al The Journal of Clinical Investigation* **2013**, *123*, 2948-2960; Sun S. *et al The Journal of Clinical Investigation* **2010**, *120*, 2715-2730). Anti-androgens such as bicalutamide and enzalutamide target AR LBD, but have no effect on truncated constitutively active AR-Vs such as AR-V7 (Li Y. *et al Cancer Research* **2013**, *73*, 483-489). Expression of AR-V7 is associated with resistance to current hormone therapies (Li Y. *et al Cancer Research* **2013**, *73*, 483-489; Antonarakis E. S. *et al The New England Journal of Medicine* **2014**, *371*, 1028-1038).

[12] While significant advances have been made in this field, there remains a need for improved treatment for AR-mediated disorders including prostate cancer, especially metastatic castration-resistant prostate cancer. Development of compounds, via unique interactions with AR NTD, would provide patients alternative options and new hope.

SUMMARY ~~OF THE INVENTION~~

[12a] In an aspect of the present disclosure, there is provided a compound having the structure of formula (A-I):



(A-I)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, wherein:

C is a 5- to 7-membered monocyclic heteroaryl comprising 1, 2, or 3 heteroatoms selected from O, S, or N as a ring member;

X is a bond, $-(CR^5R^6)_t-$, or $-NR^7-$;

Y is a bond, $-CH_2-$, $-C(CH_3)H-$, -O-, -S-, -NH-, $-NCH_3-$, or $-N(COCH_3)-$;

Z is a bond, $-CH_2-$, -O-, or -NH-;

W is a bond, $-CH_2-$, $-C(CH_3)H-$, -C(=O)-, $-N(R^7)CO-$, or $-CONR^7-$;

V is $-CH_2-$ and L is halogen, $-NH_2$, or $-CF_3$; or

V is $-CH_2CH_2-$ and L is halogen or $-NH_2$;

R^1 and R^2 are each independently hydrogen, halogen, -CN, $-CF_3$, methyl, or $–CONH_2$;

R^3 is selected from -CN, C_1-C_3 alkoxy, $-CF_3$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, $-S(C_1$-C_3 alkyl), $-SO_2(C_1$-C_3 alkyl), $-NH_2$, $-(C_1$-C_3 alkyl)NH_2, $-NHSO_2CH_3$, $-NHSO_2CF_3$, $-N(CH_3)SO_2CH_3$, $-NHSO_2CH_2CH_3$, $-N(CH_3)SO_2CH_2CH_3$, $-CH_2NHSO_2CH_3$, $-CH_2N(CH_3)SO_2CH_3$, $-SO_2NH_2$, $-CONH_2$, $-CON(C_1$-C_3 alkyl)$_2$, $-CONH(C_1$-C_3 alkyl), $-NHCO(C_1$-C_3 alkyl), $-N(CH_3)COO(C_1$-C_3 alkyl), $-NHCO(C_1$-C_3 alkyl), or $-N(CH_3)COO(C_1$-C_3 alkyl);

R^5 and R^6 are each independently hydrogen, halogen, -OH, or C_1-C_3 alkyl;

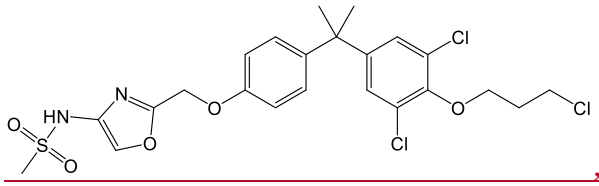
R^7 is H or C_1-C_6 alkyl;

n1 and n2 are each independently 0, 1, or 2;

n3 is 1, 2, 3, 4 or 5; and

t is 0, 1 or 2.

[12b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of: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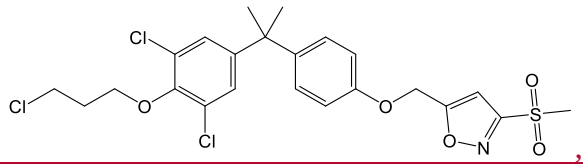
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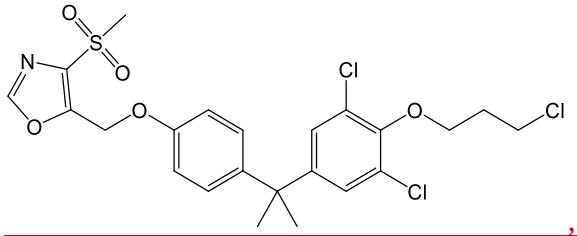
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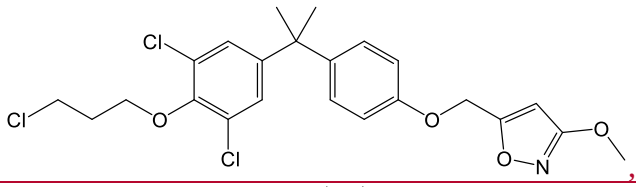
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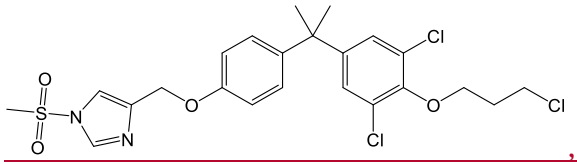
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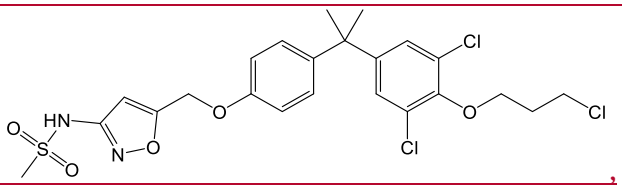
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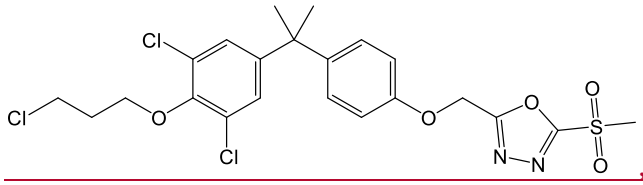
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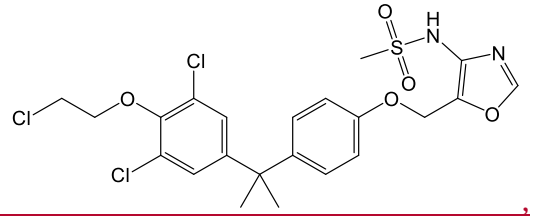
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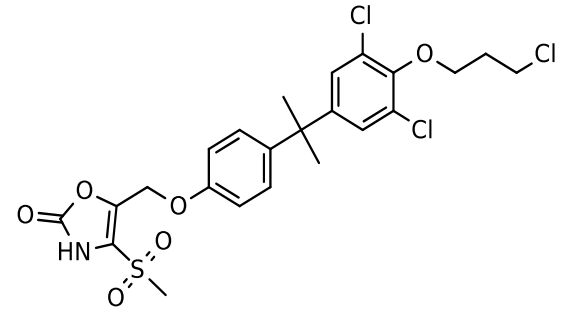
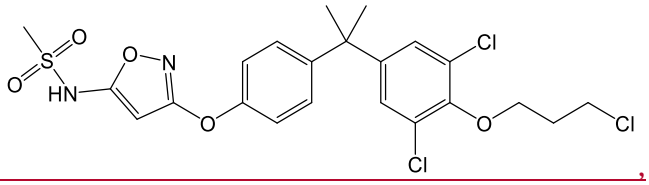
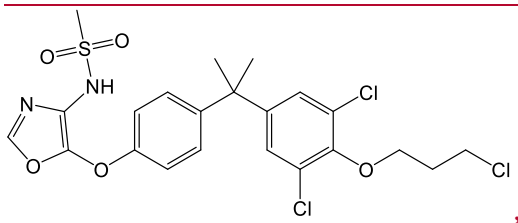
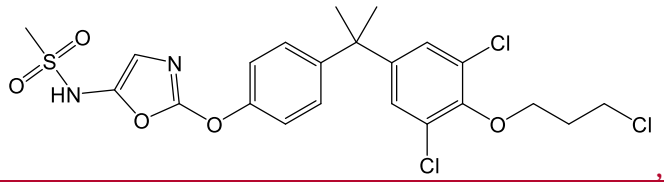
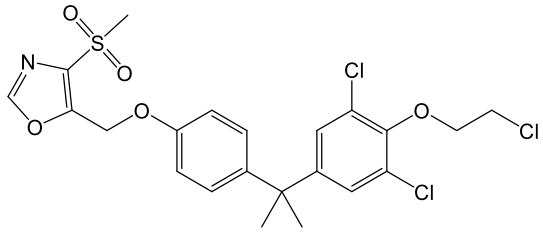
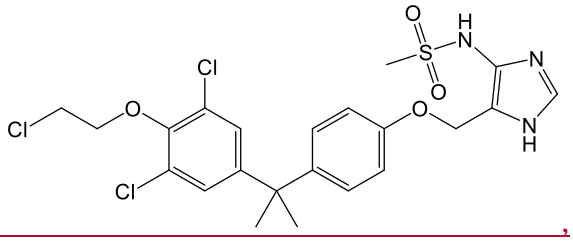
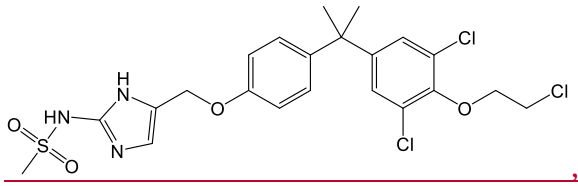
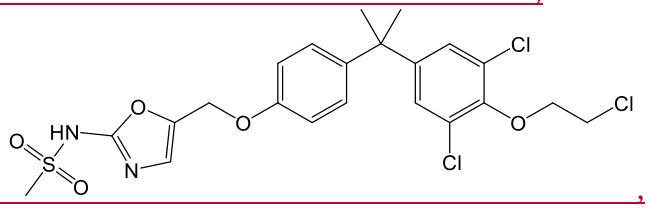
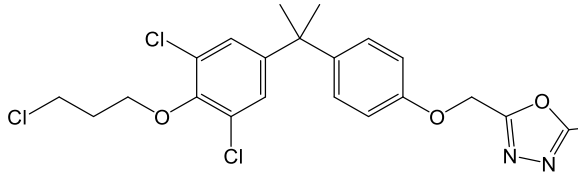
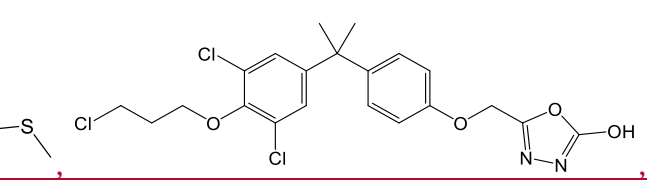
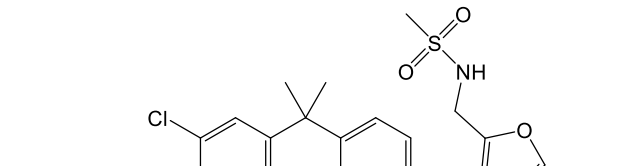
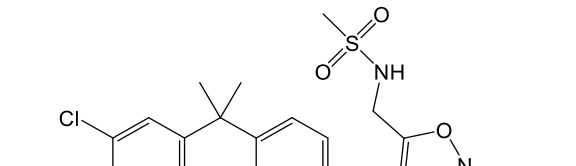

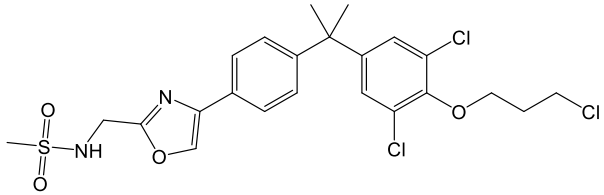
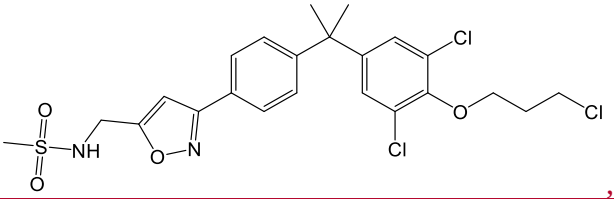

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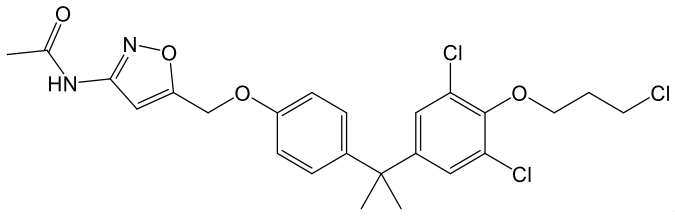
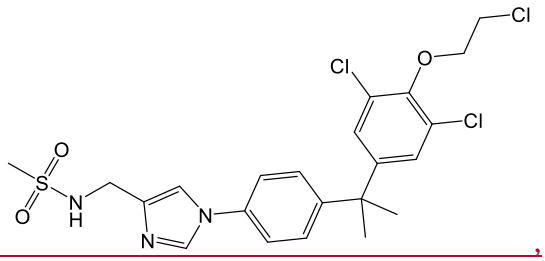
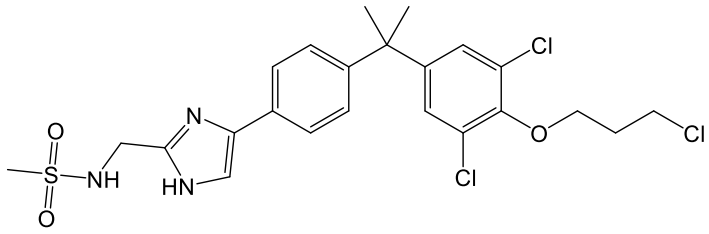
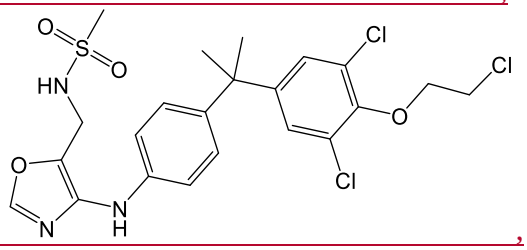
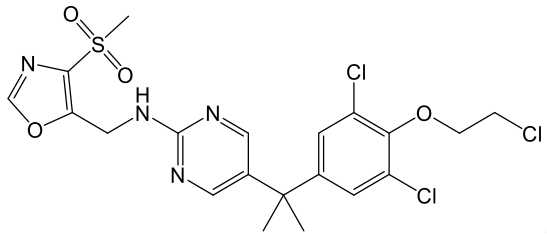
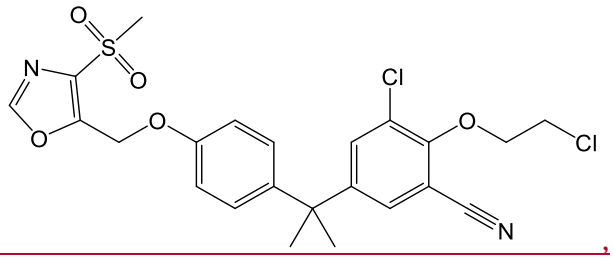
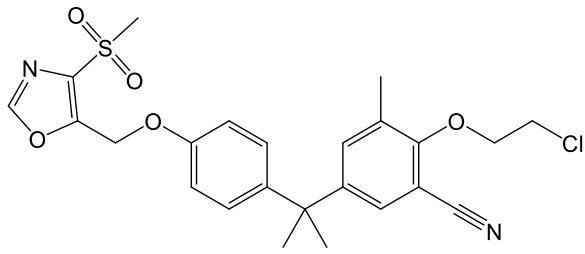
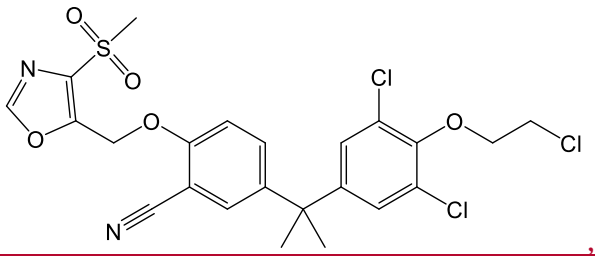
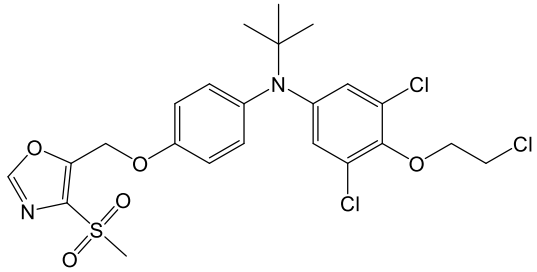
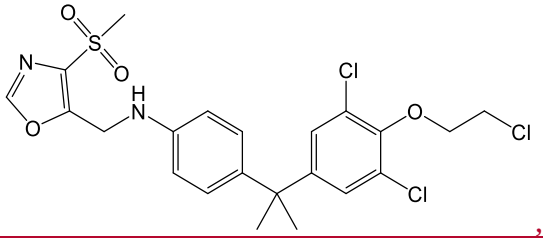
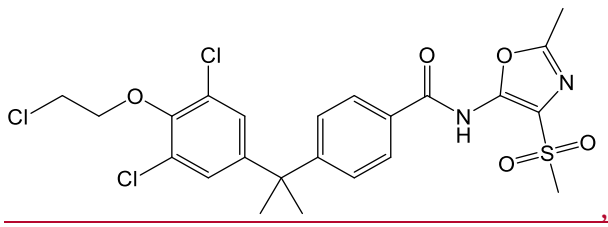
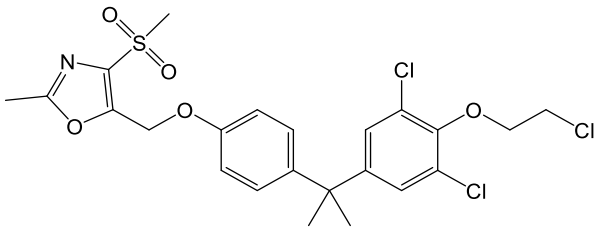
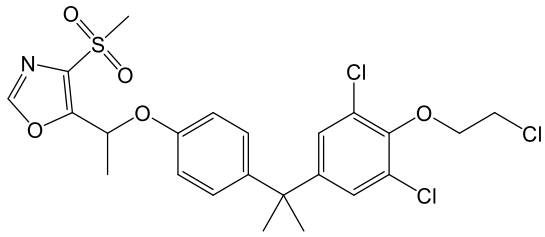
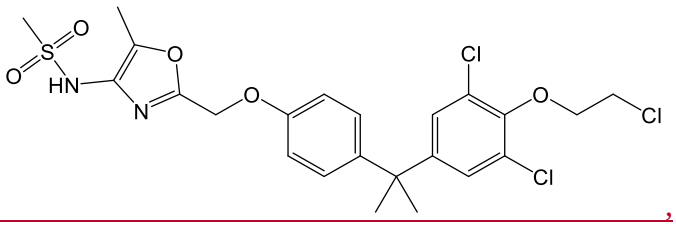

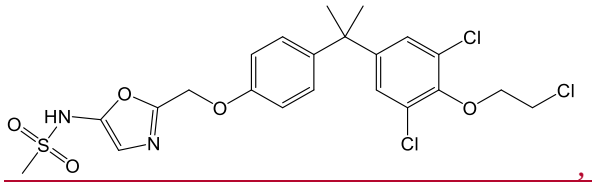
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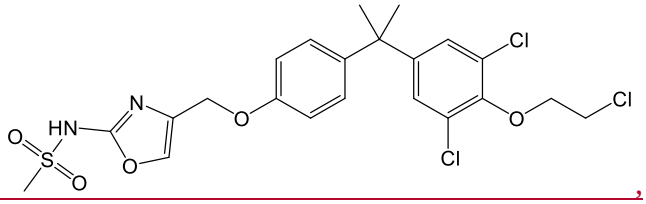
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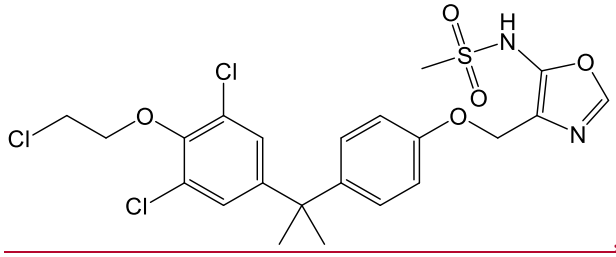
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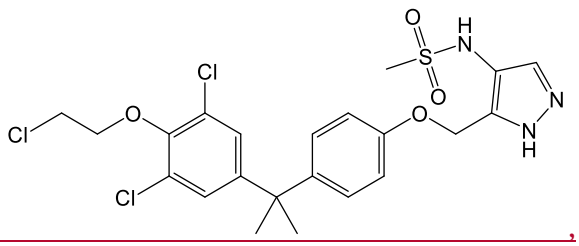
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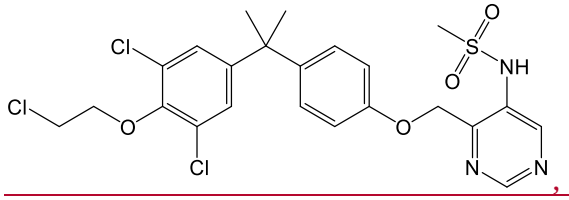
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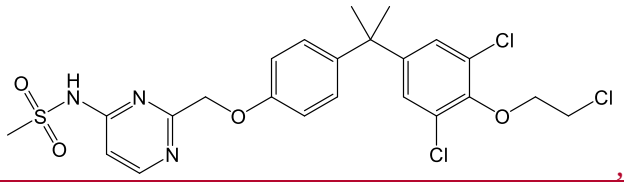
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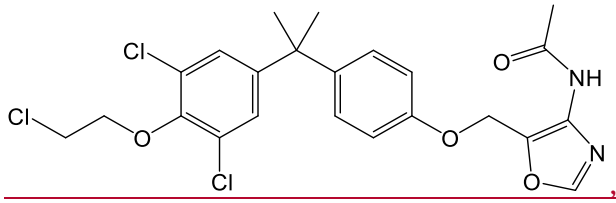
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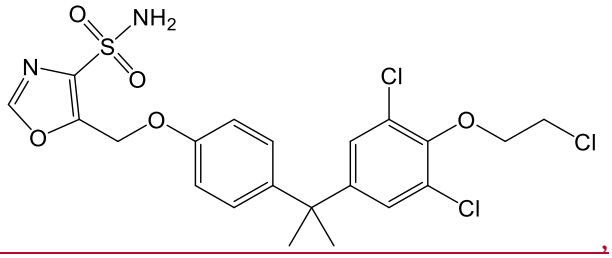
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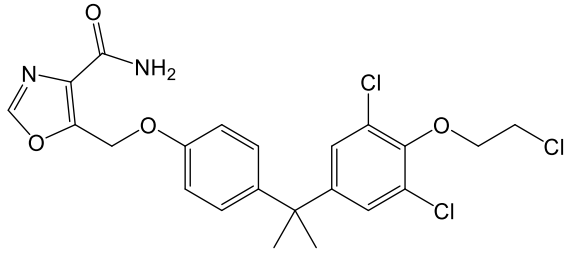
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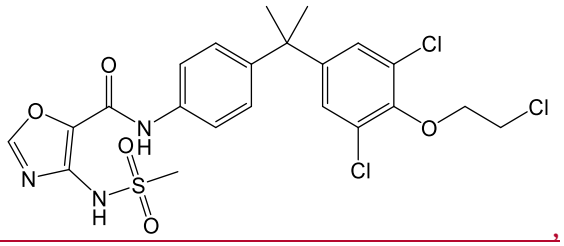
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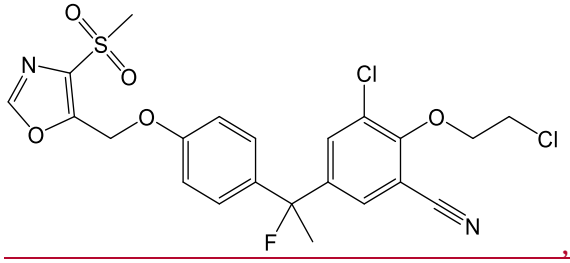
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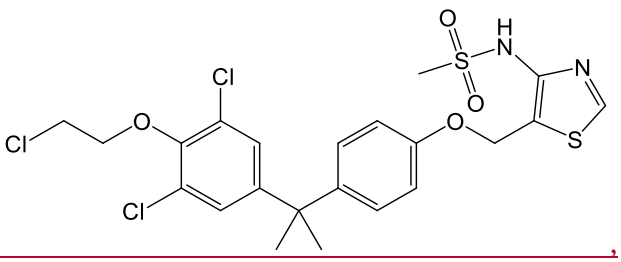
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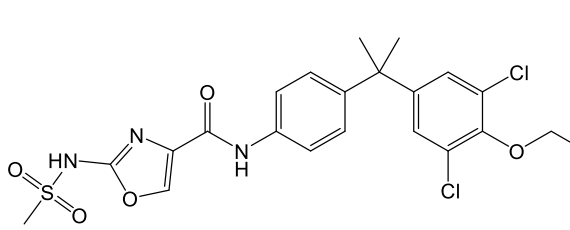
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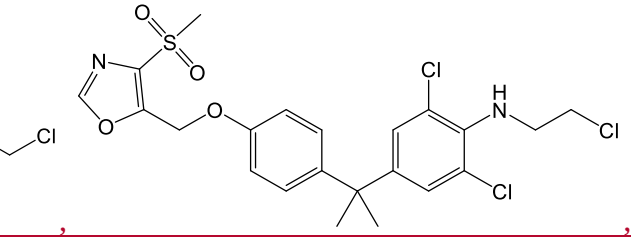
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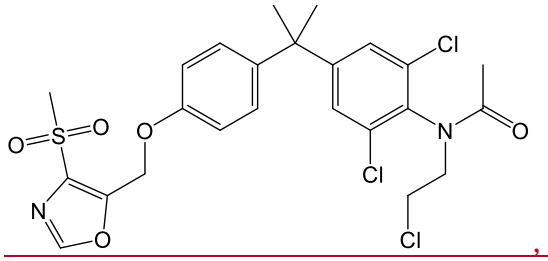
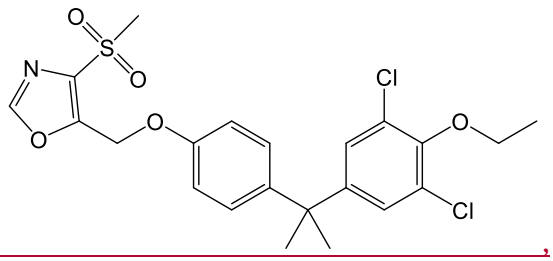
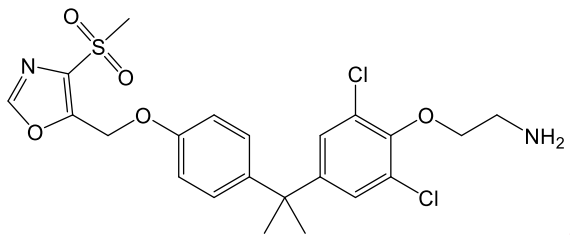
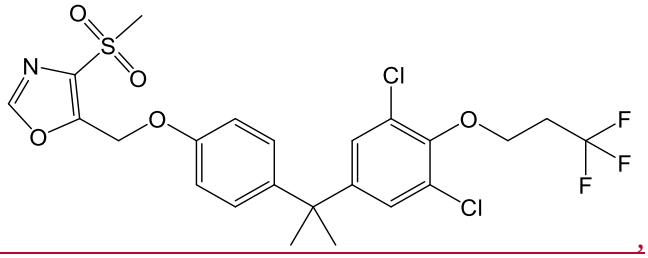
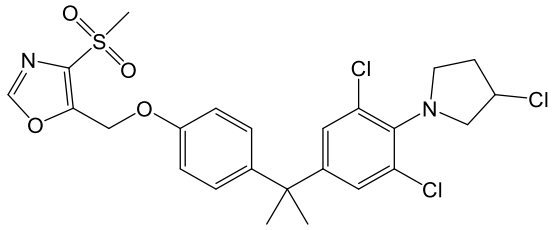
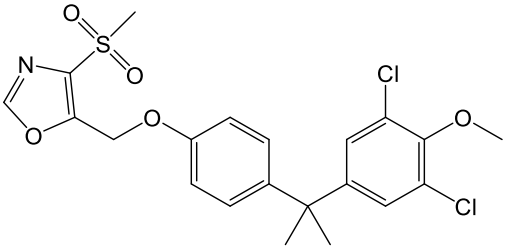
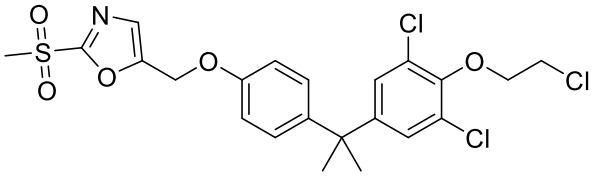
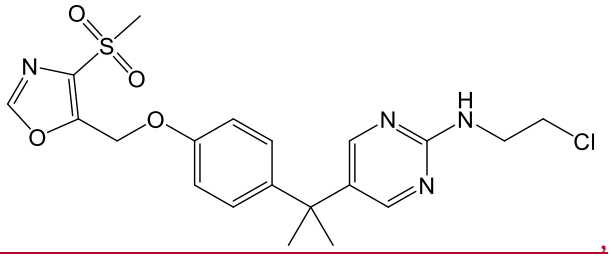
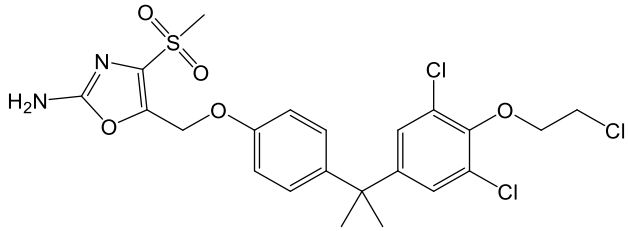
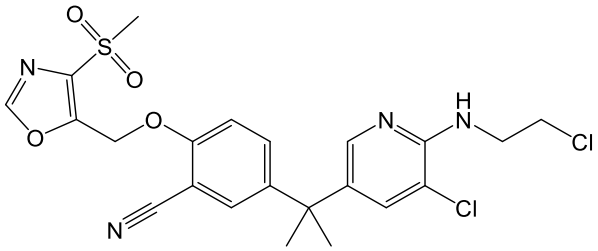
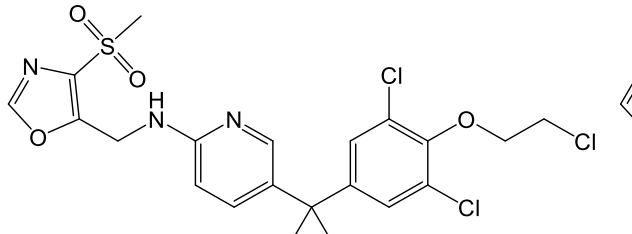
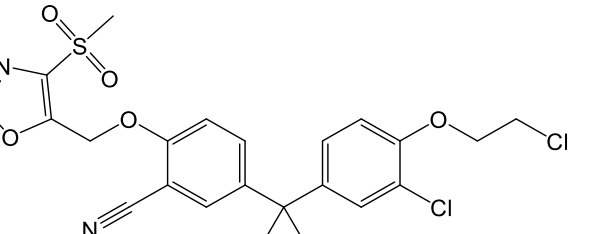

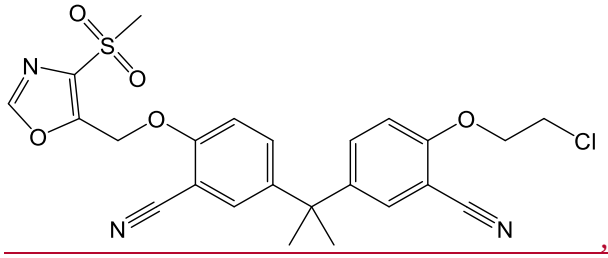
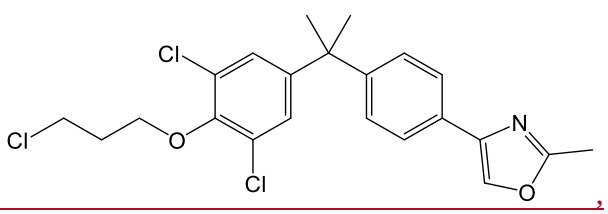

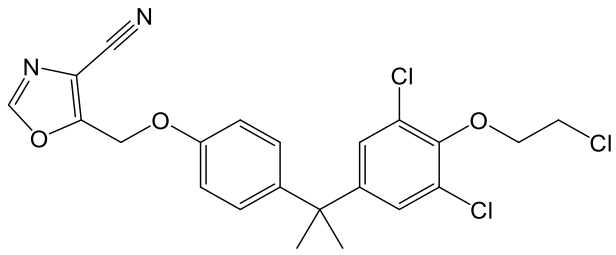
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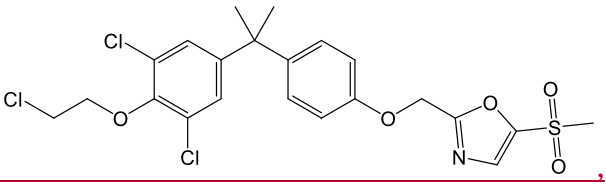
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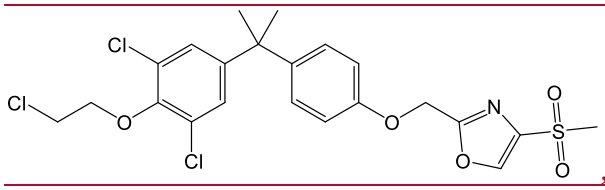
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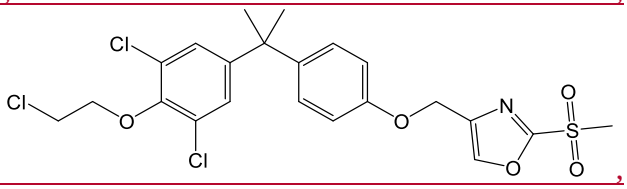
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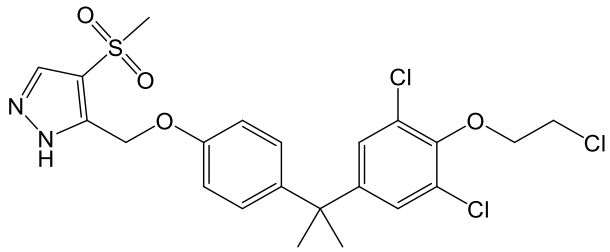
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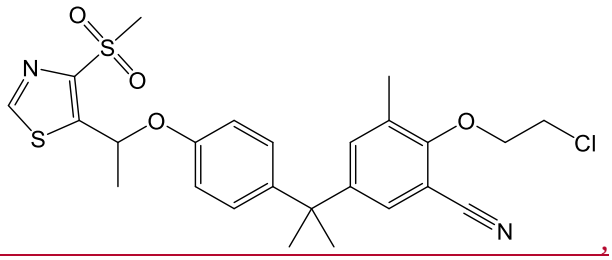
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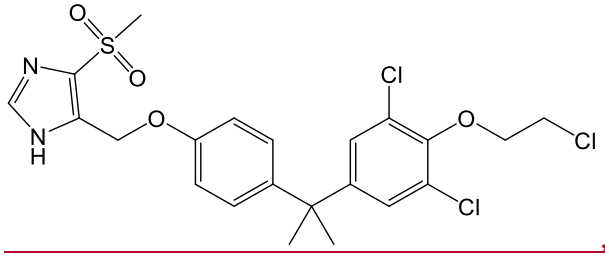
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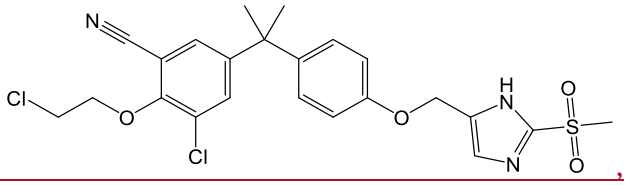
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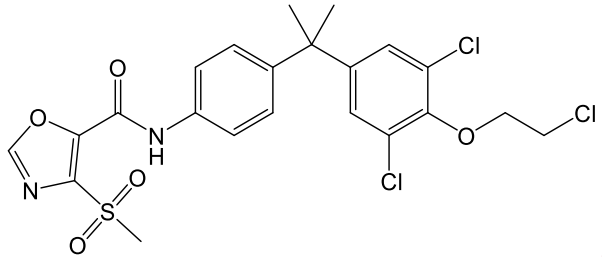
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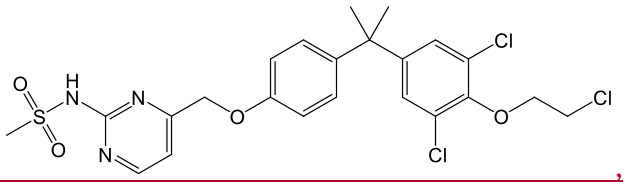
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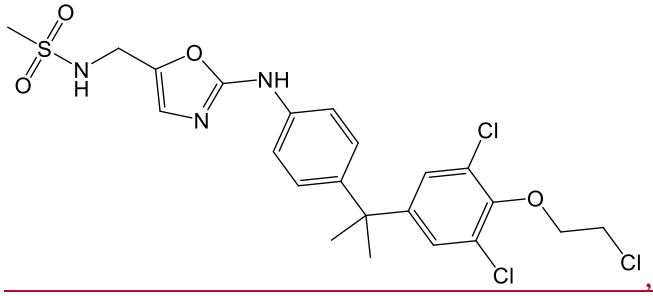
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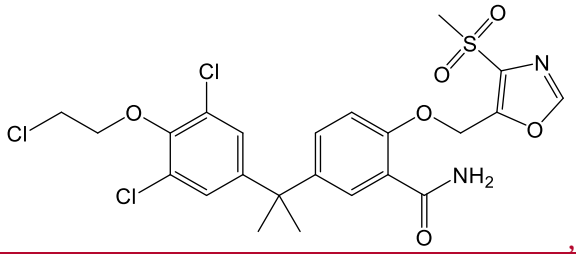
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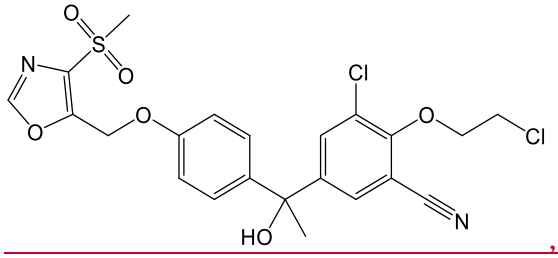
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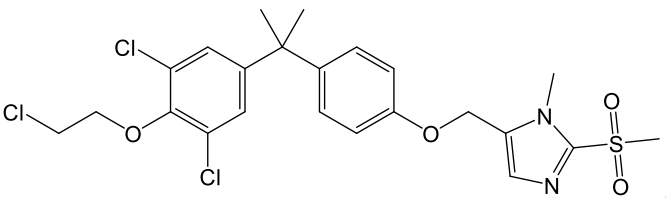
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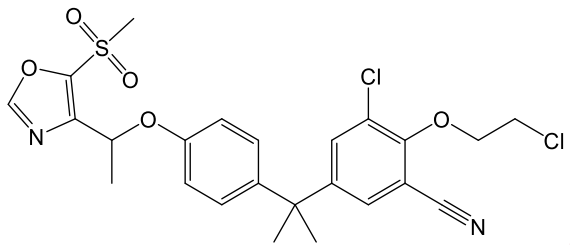
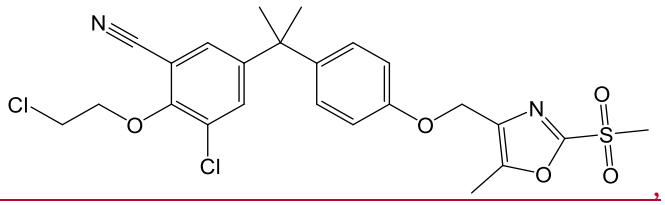
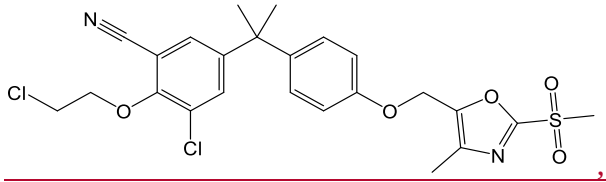
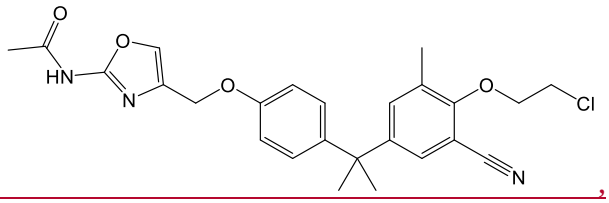
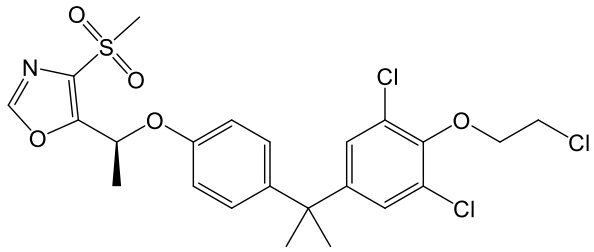
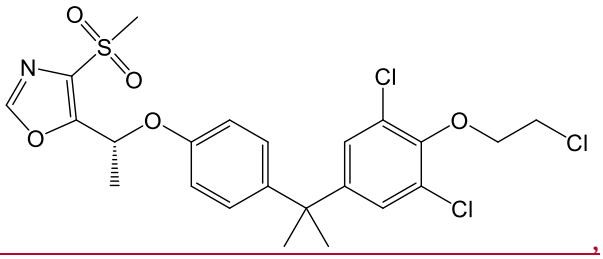
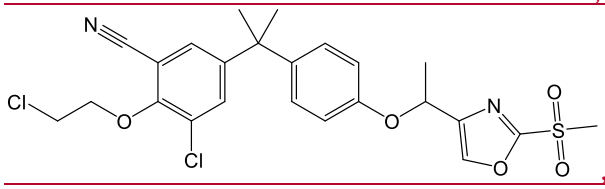
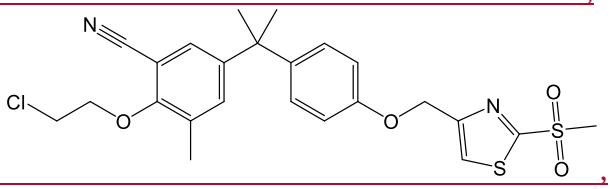
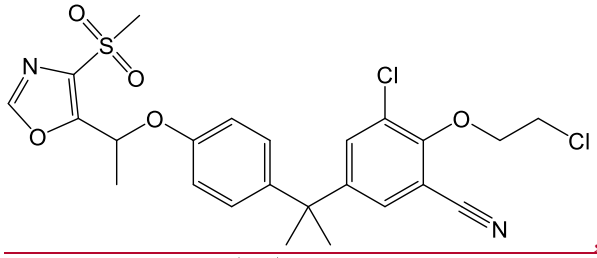
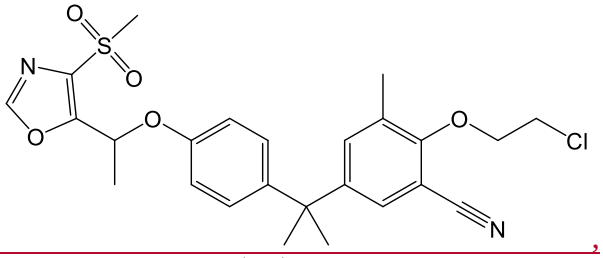
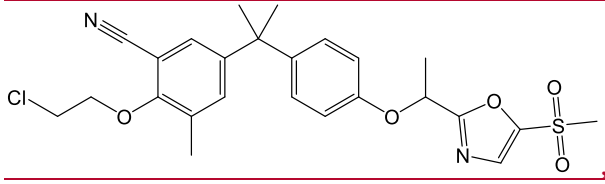
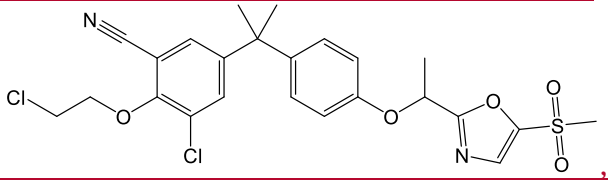
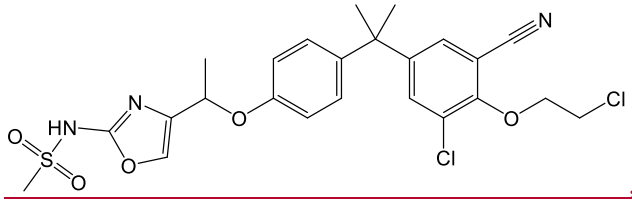
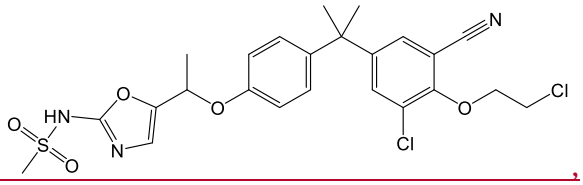
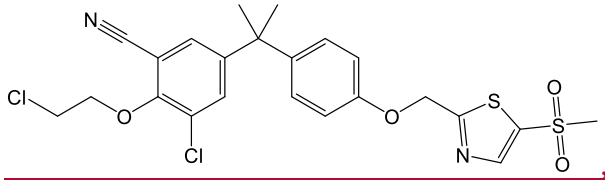
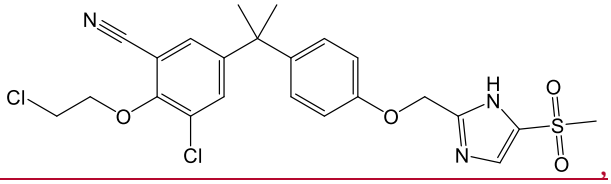

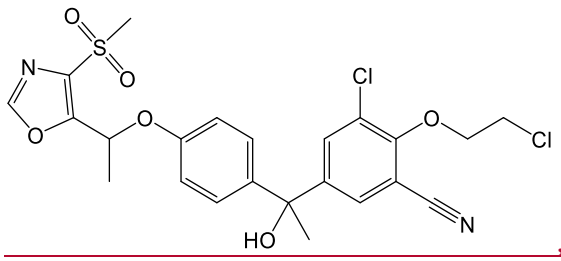
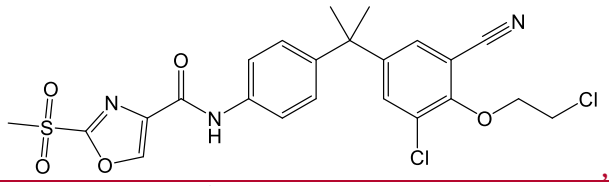

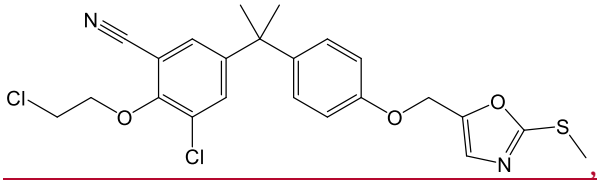
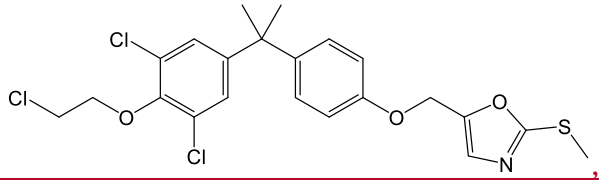
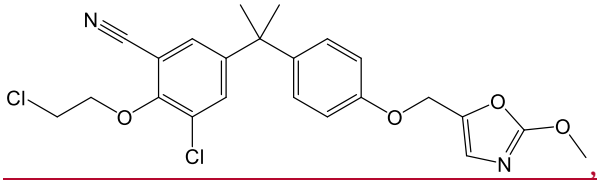
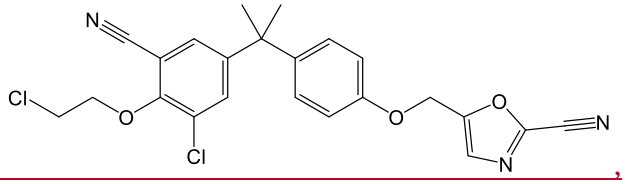
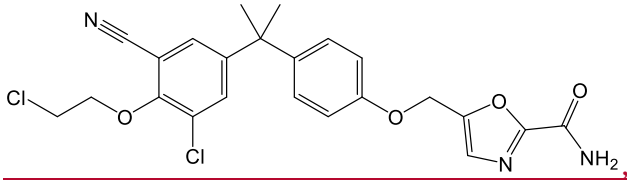
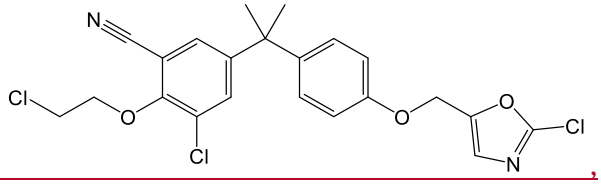
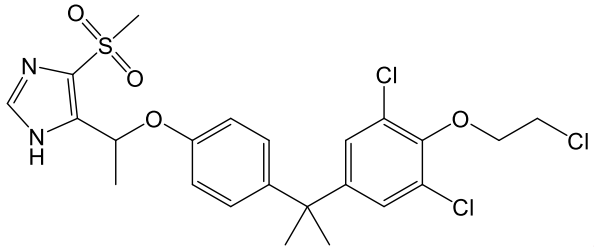
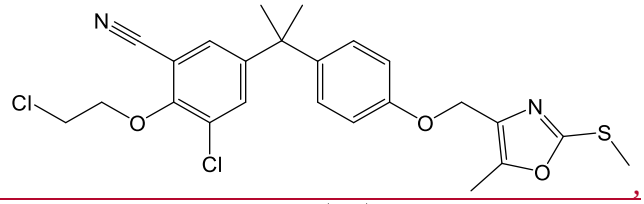
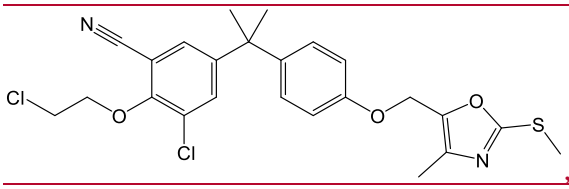
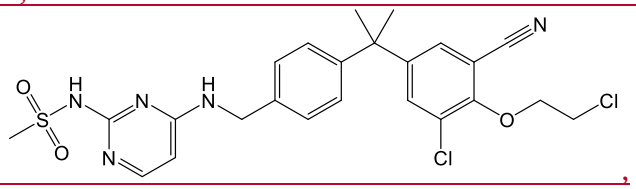
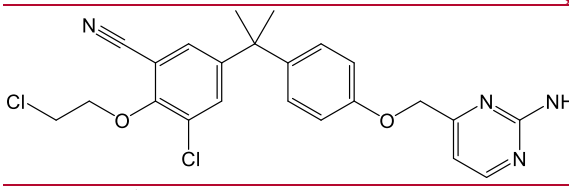
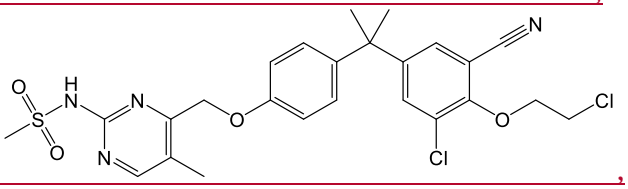
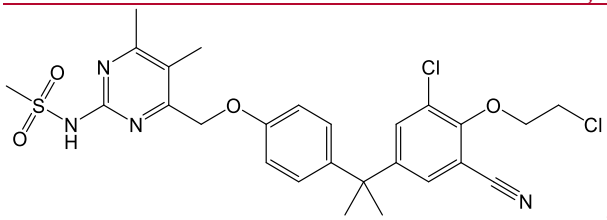
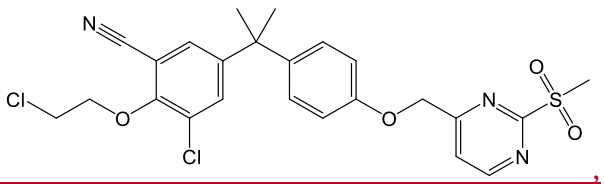
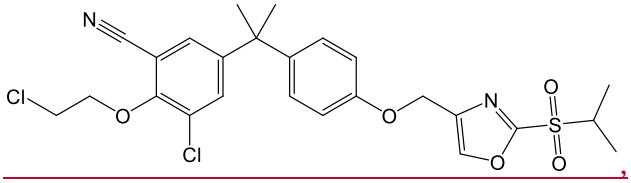

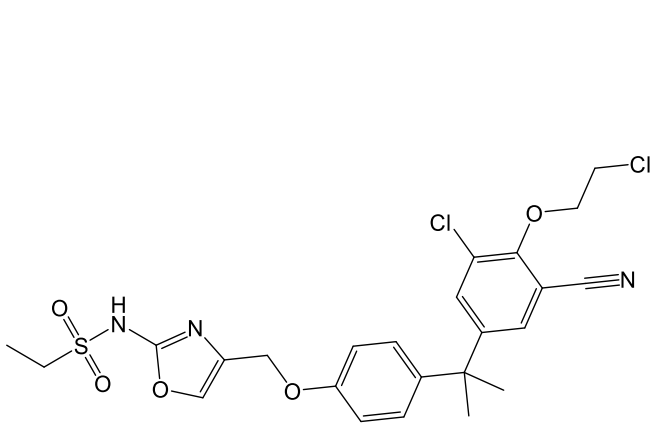
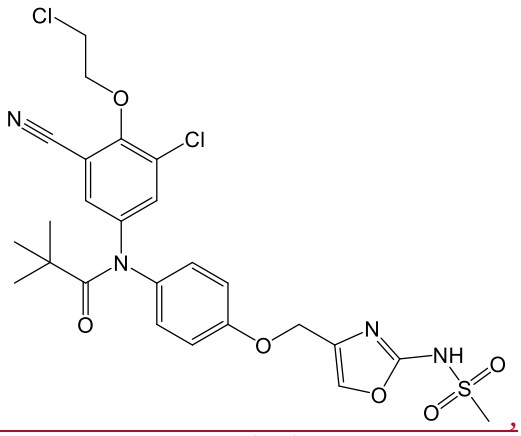

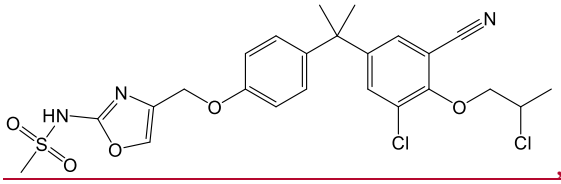
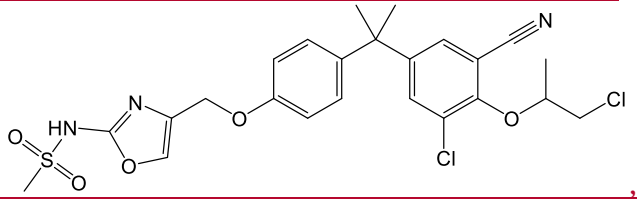

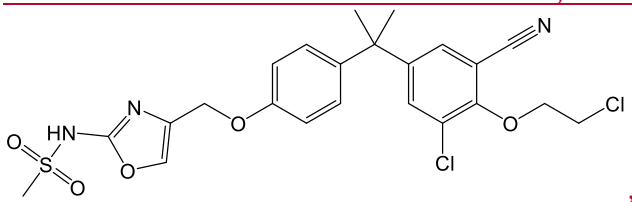
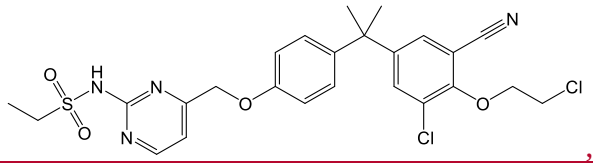

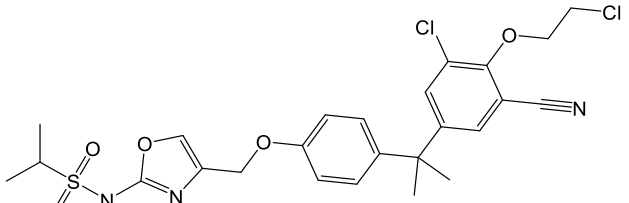

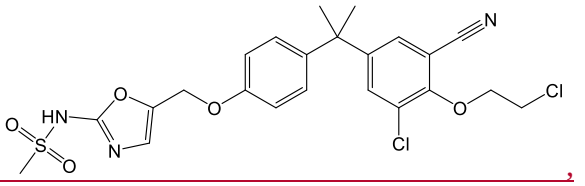

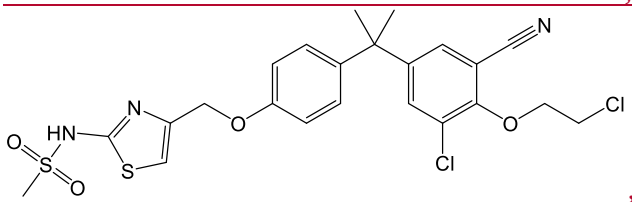

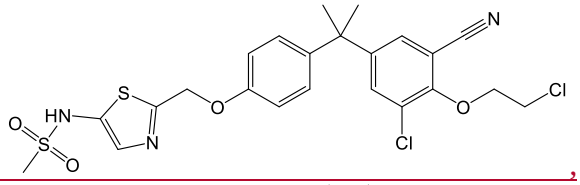

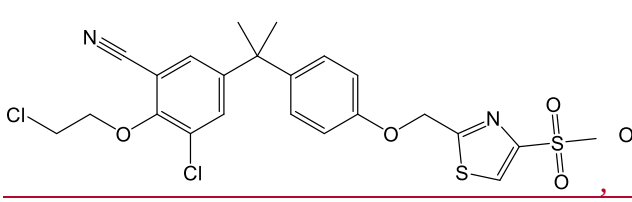

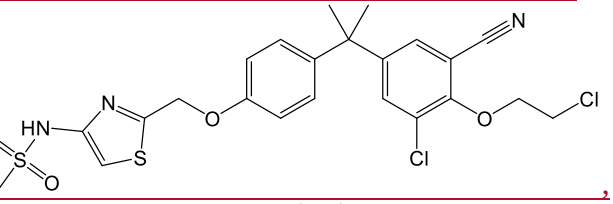

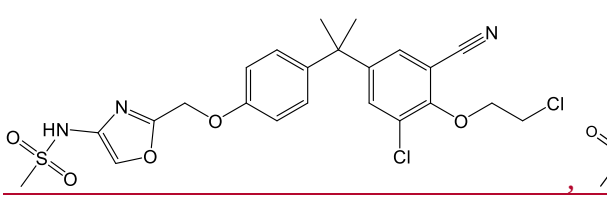
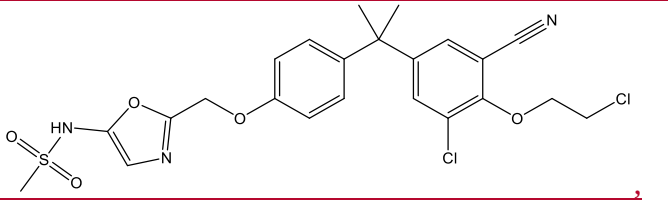

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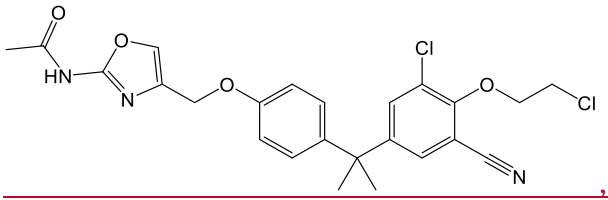
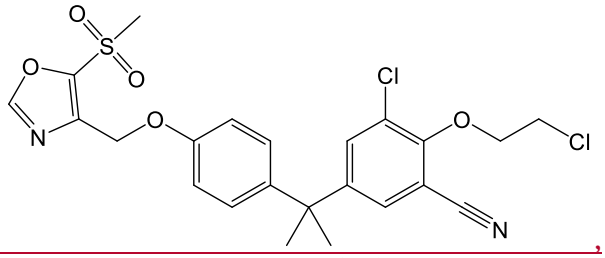

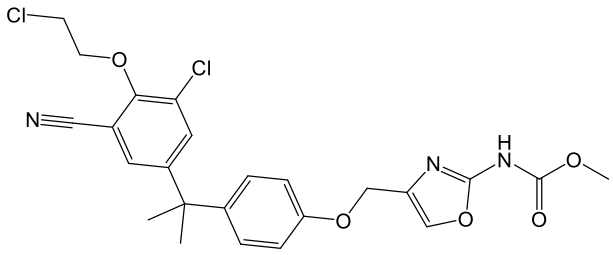
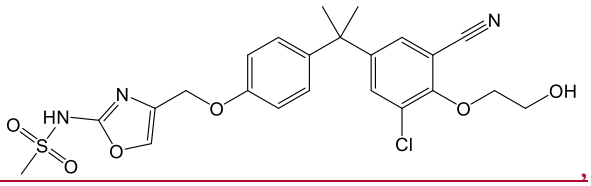
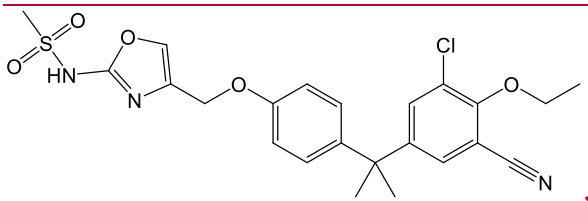
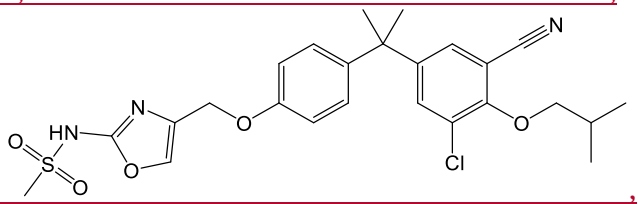
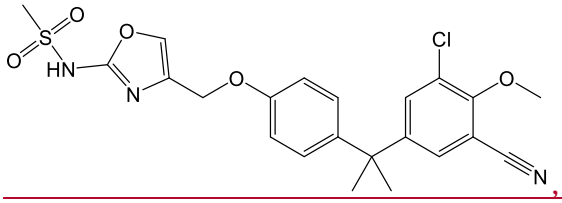
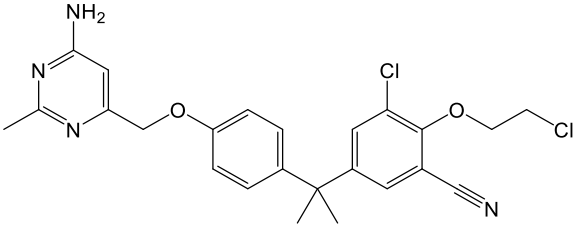
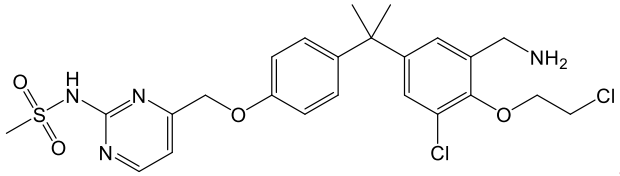
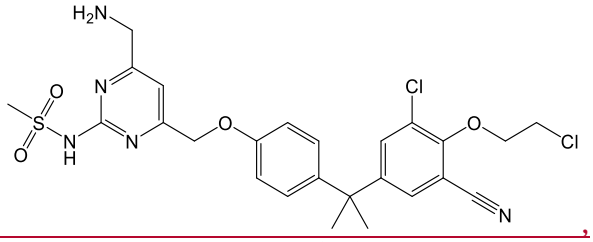
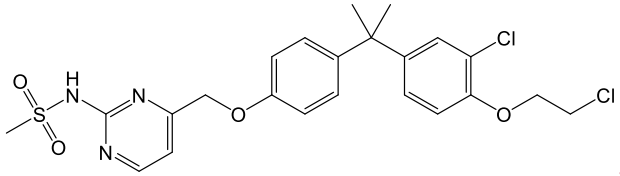
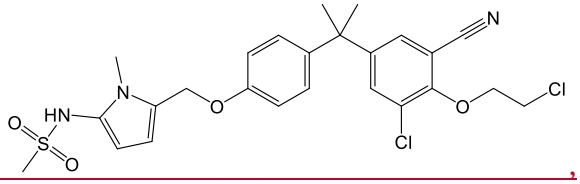
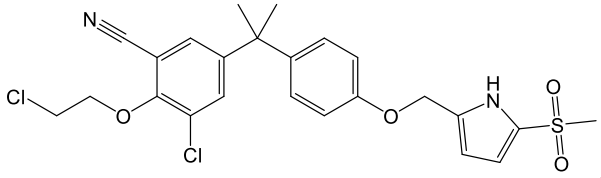
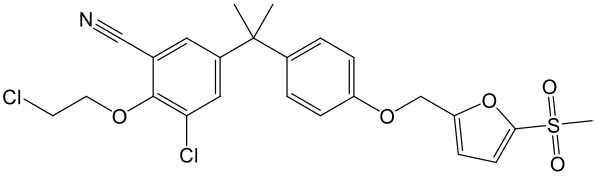
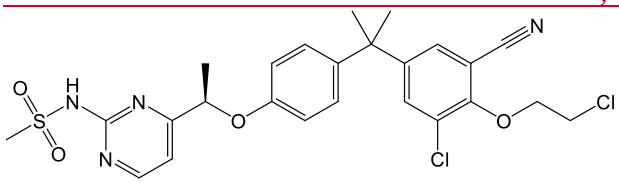
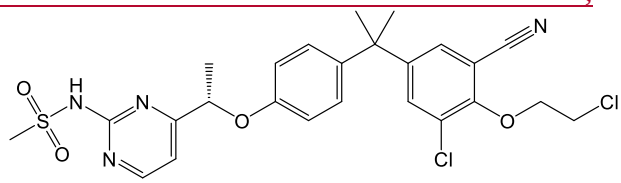
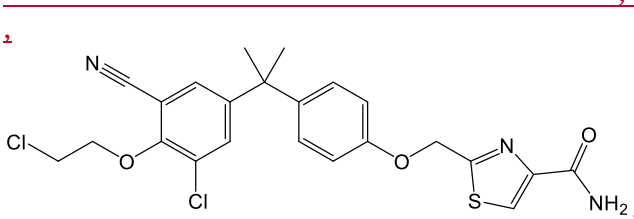
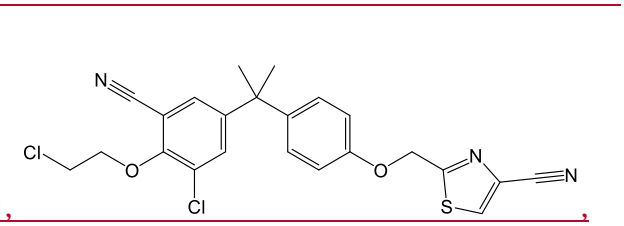

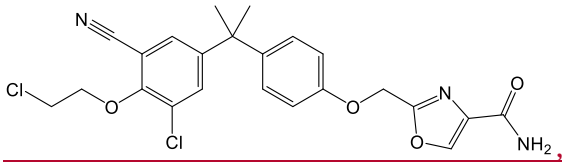
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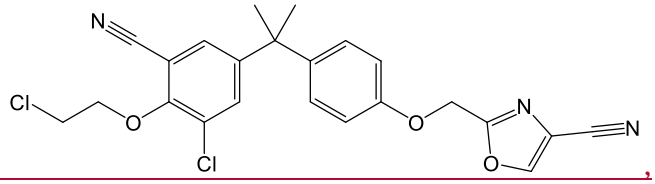
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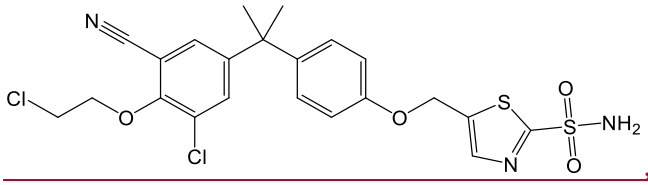
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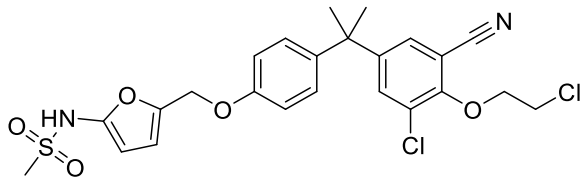
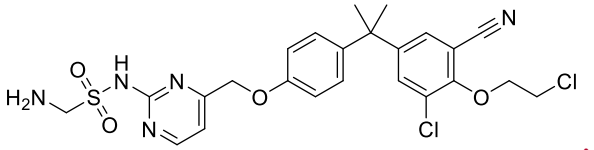
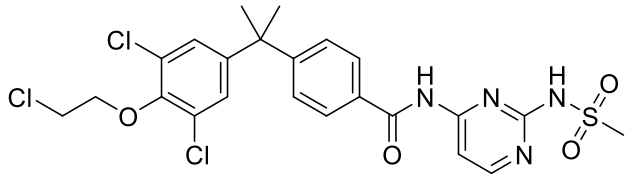
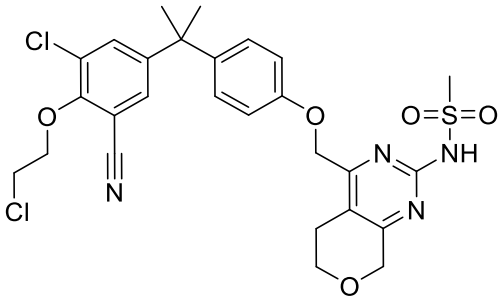
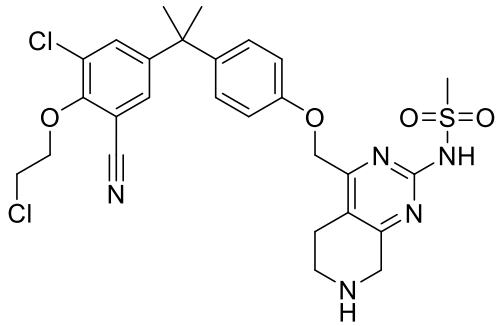
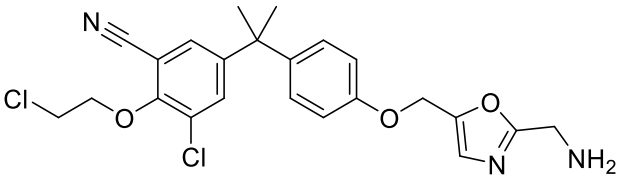
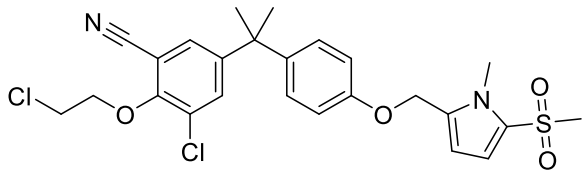
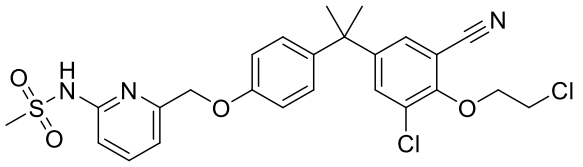
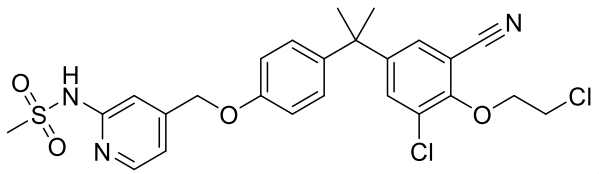
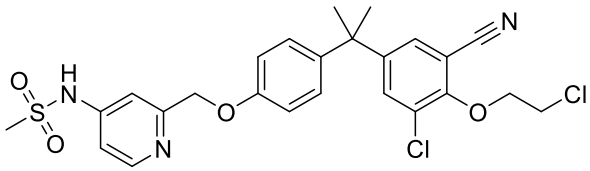
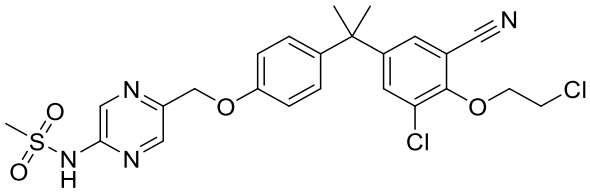
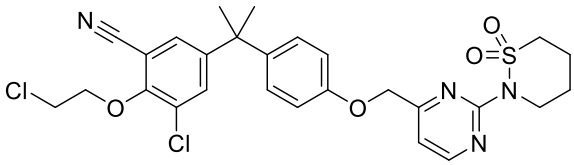
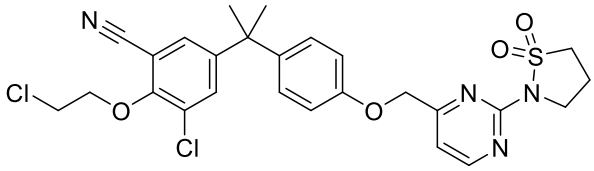

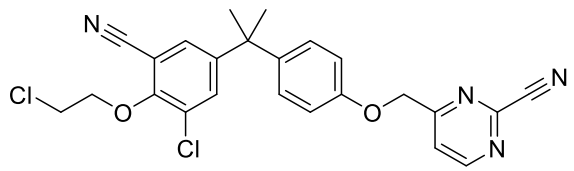

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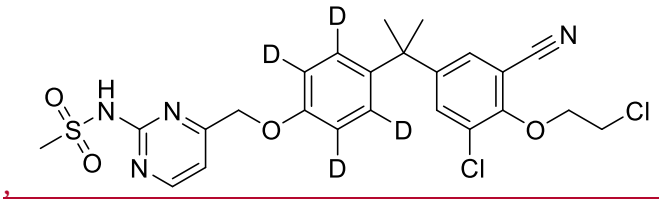
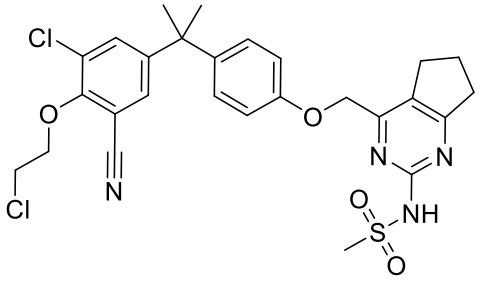
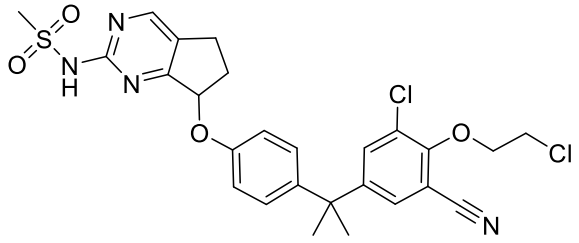
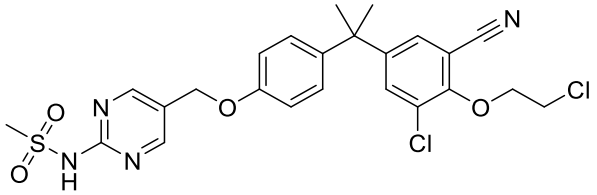
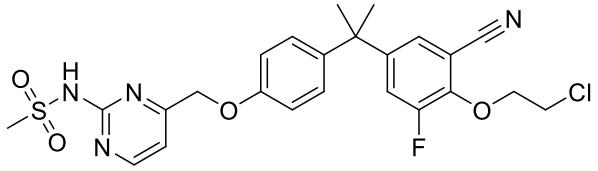
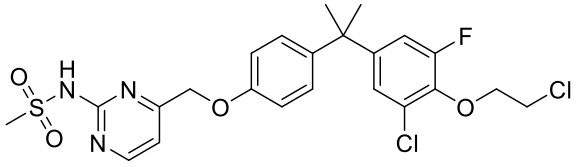


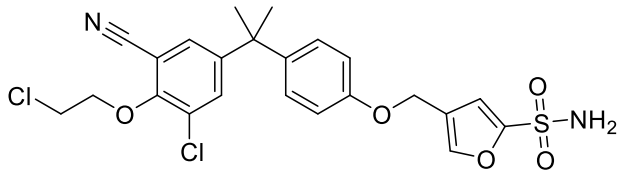


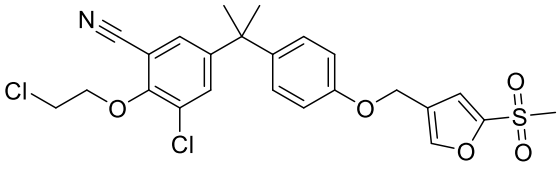


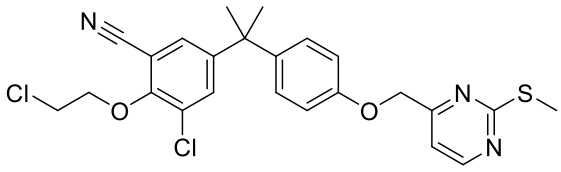


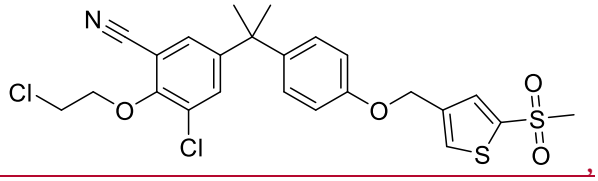


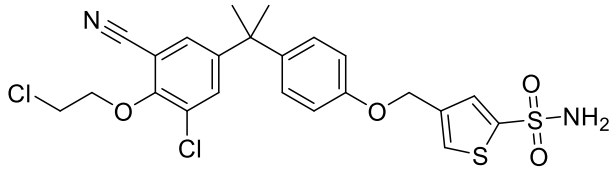


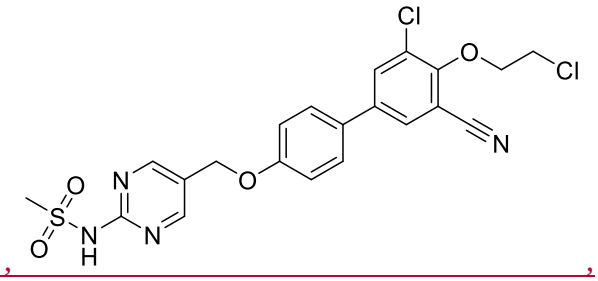


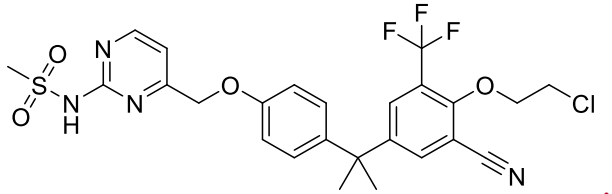


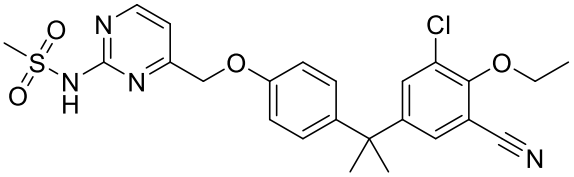


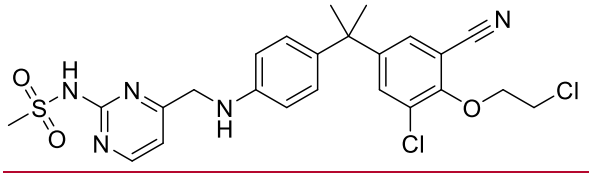


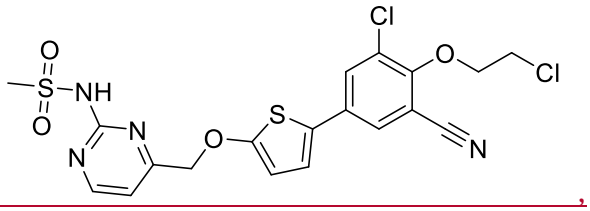


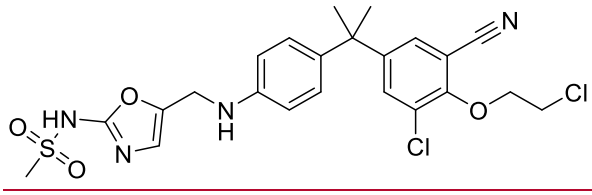


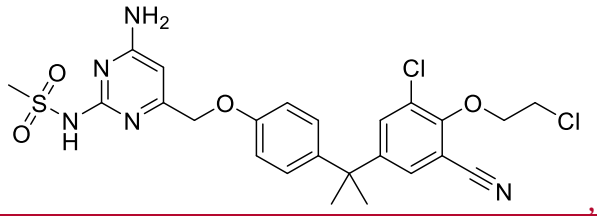


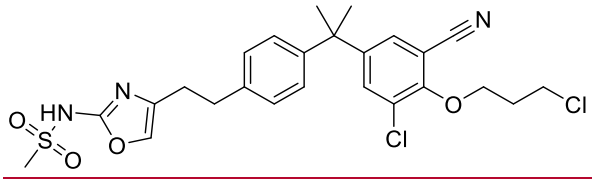


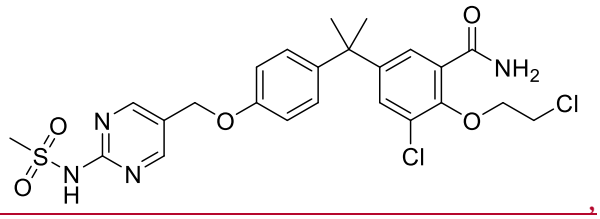


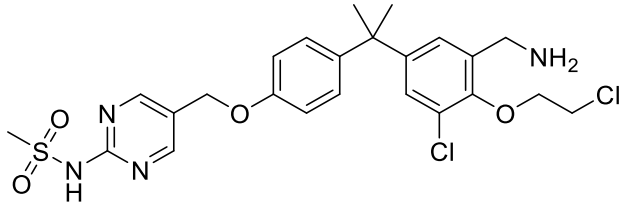


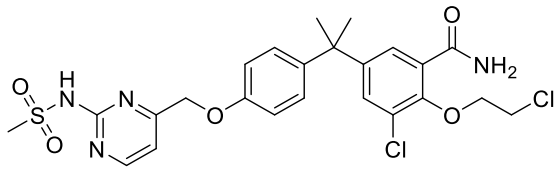


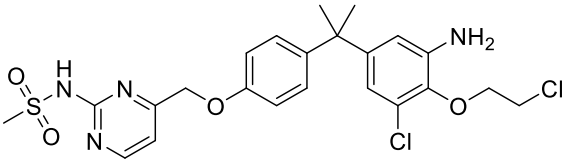


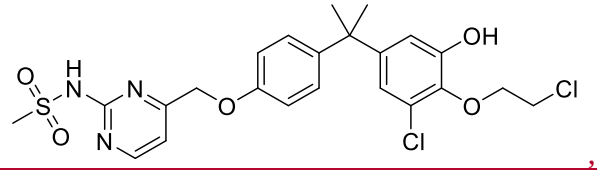


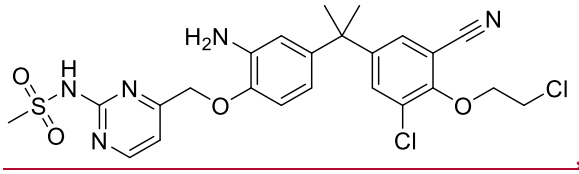


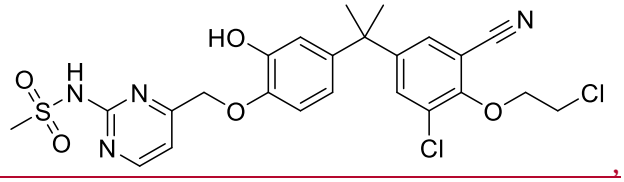


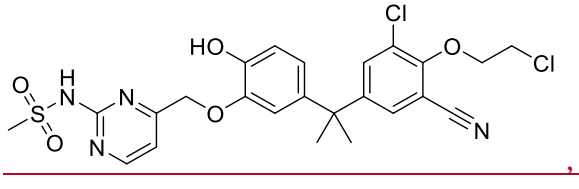


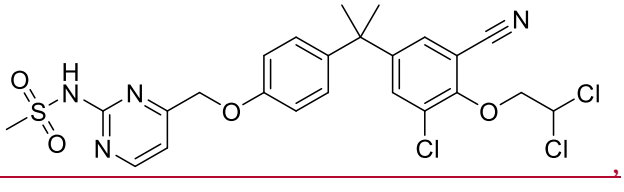


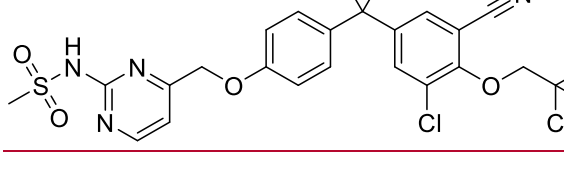


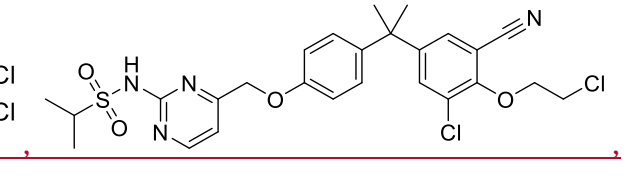


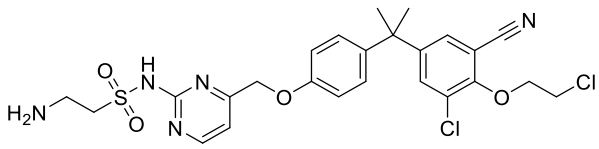
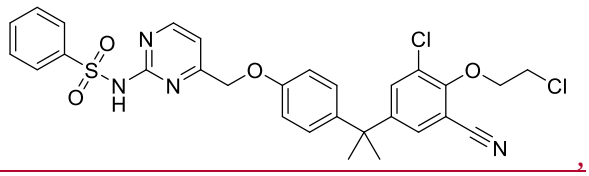
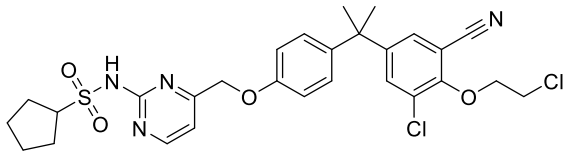
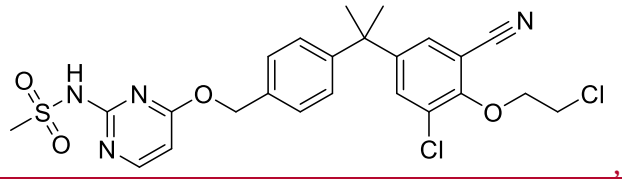










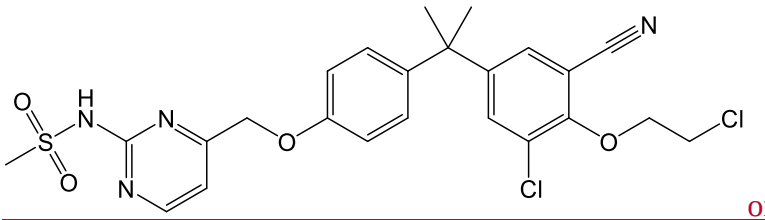





or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

[12c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

[12d] In another aspect of the present disclosure, there is provided a use of a compound, pharmaceutically acceptable salt, tautomer, or stereoisomer of the compound disclosed herein, in the manufacture of a medicament for treating cancer.

[12e] In a further aspect of the present disclosure, there is provided a compound having the structure:



or a pharmaceutically acceptable salt thereof.

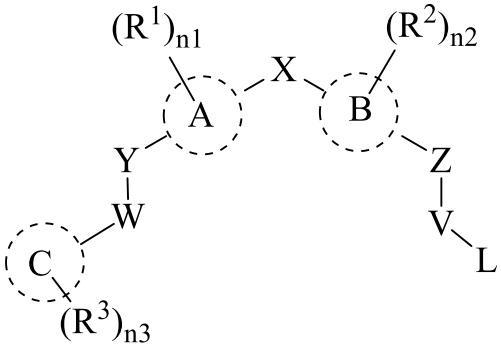
[12f] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt of the compound disclosed herein, and a pharmaceutically acceptable carrier.

[12g] In a further aspect of the present disclosure, there is provided a use of a compound or a pharmaceutically acceptable salt of the compound disclosed herein, in the manufacture of a medicament for treating prostate cancer.

[12h] In another aspect of the present disclosure, there is provided a compound, pharmaceutically acceptable salt, tautomer, or stereoisomer of the compound disclosed herein, for use in therapy.

[13] The compounds of the present disclosure are androgen receptor modulators which may be useful in treating various diseases and conditions as disclosed herein. In one

~~embodiment~~example, the present disclosure provides compounds comprising the structure of formula (IIIA):



(IIIA)

[14] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[15] A and B are each independently selected from phenyl, pyridyl, pyrimidyl, or thiophene;

[16] C is a 3- to 10-membered ring;

[17] X is a bond, $-(CR^5R^6)_t-$, or $-NR^7$;

[18] Y is a bond, $-(CR^8R^9)_m-$, -O-, -S-, -S(=O)-, $-SO_2-$, $-NR^7-$, or $-N(COCH_3)-$;

[33] R^{13}, R^{14} and R^{15} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form a 3- to 6-membered heterocyclyl;

[34] R^{16} is hydrogen, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, C_3-C_6 cycloalky, or phenyl;

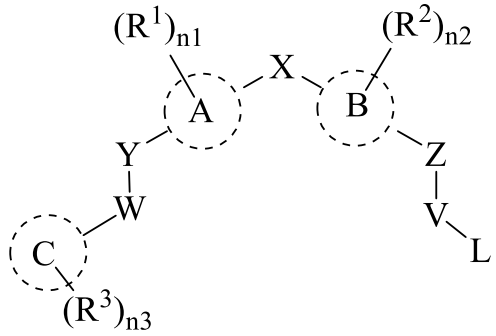
[35] each m is independently 0, 1, or 2;

[36] n1 and n2 are each independently 0, 1, or 2;

[37] n3 is 1, 2, 3, 4 or 5; and

[38] t is 0, 1 or 2.

[39] In one ~~embodiment~~example, the present disclosure provides compounds comprising the structure of formula (IVA):



(IVA)

[40] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[41] A and B are each independently selected from phenyl, pyridyl, pyrimidyl, or thiophene;

[42] C is a 3- to 10-membered ring;

[43] X is a bond, -$(CR^5R^6)_t$-, or -NR^7-;

[44] Y and Z are each independently a bond, -CH_2-, -$C(CH_3)H$-, -O-, -S-, -NH-, -NCH_3-, or –$N(COCH_3)$-;

[45] W is a bond, -CH_2-, -$C(CH_3)H$-, -C(=O)-, -$N(R^7)CO$-, or -$CONR^7$-;

[46] V is -CH_2- and L is halogen, -NH_2, or -CF_3; or

[47] V is -CH_2CH_2- and L is halogen or -NH_2;

[48] R^1 and R^2 are each independently hydrogen, halogen, -CN, -CF_3, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted –(C_1-C_6 alkyl)-(C_1-C_6 alkoxy), optionally substituted –(C_1-C_6 alkyl)-OH, -$NR^{13}R^{14}$, optionally substituted –(C_1-C_6 alkyl)-$NR^{13}R^{14}$, -$NR^{14}SO_2R^{16}$, optionally substituted -(C_1-C_6 alkyl)$NR^{14}SO_2R^{16}$, -$NR^{14}COR^{16}$, optionally substituted -(C_1-C_6 alkyl)-$NR^{14}COR^{16}$, -$CONR^{13}R^{14}$, optionally substituted -(C_1-C_6 alkyl)-$CONR^{14}R^{15}$, -

$SO_2NR^{14}R^{15}$, optionally substituted -(C_1-C_6 alkyl)-$SO_2NR^{14}R^{15}$, optionally substituted -SO_2R^{16} or optionally substituted -(C_1-C_6 alkyl)-SO_2R^{16};

[49] R^3 is selected from halogen, oxo, =S, =NR^{16}, -CN, -CF_3, -OH, -S(C_1-C_3 alkyl), C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, -$NR^{13}R^{14}$, –(C_1-C_3 alkyl)-$NR^{13}R^{14}$, -$NR^{14}SO_2R^{16}$, -(C_1-C_3 alkyl)$NR^{14}SO_2R^{16}$, -$NR^{14}COR^{16}$, -(C_1-C_6 alkyl)-$NR^{14}COR^{16}$, -$CONR^{14}R^{15}$, -(C_1-C_3 alkyl)-$CONR^{14}R^{15}$, -$SO_2NR^{14}R^{15}$, -(C_1-C_3 alkyl)-$SO_2NR^{14}R^{15}$, -SO_2(C_1-C_3 alkyl), or -(C_1-C_6 alkyl)-SO_2(C_1-C_3 alkyl);

[50] R^5 and R^6 are each independently hydrogen, halogen, -OH, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or C_1-C_3 alkoxy; or R^5 and R^6 taken together form an optionally substituted 3- to 6-membered carbocyclyl or heterocyclyl;

[51] R^7 is H or C_1-C_6 alkyl;

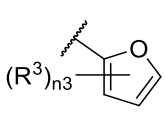
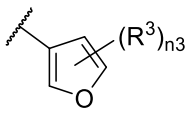
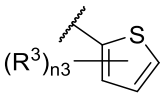
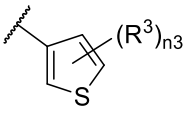
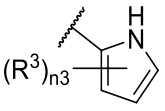
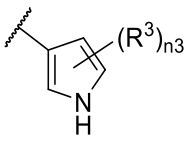
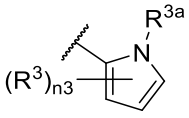
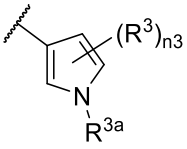
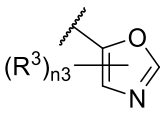
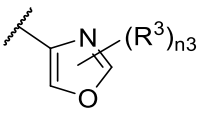
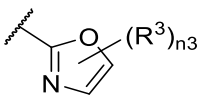
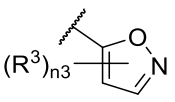
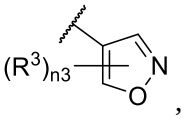
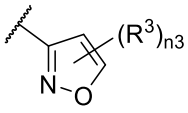
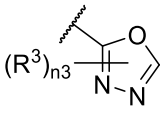
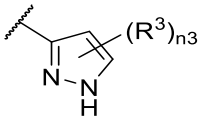
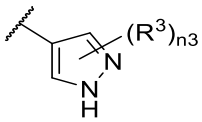
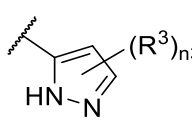
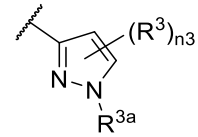
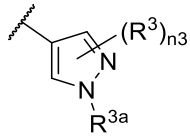
[52] R^{13}, R^{14} and R^{15} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form a 3- to 6-membered heterocyclyl;

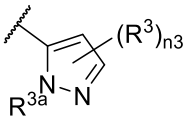
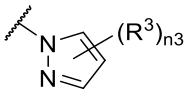
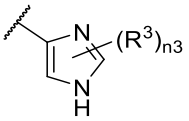
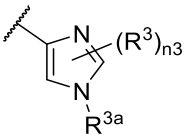
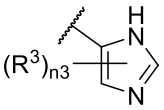
[53] R^{16} is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl;

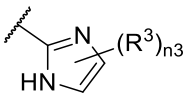
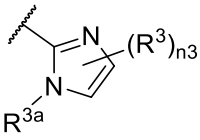
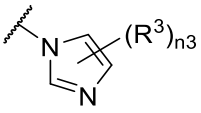
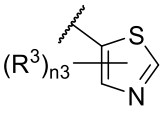
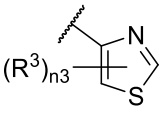
[54] n1 and n2 are each independently 0, 1, or 2;

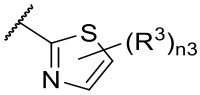
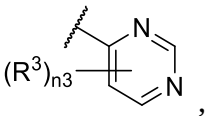
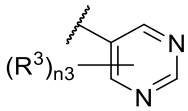
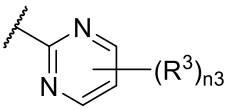
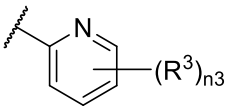
[55] n3 is 1, 2, 3, 4 or 5; and

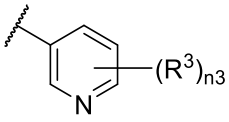
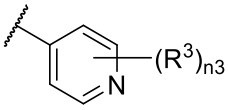
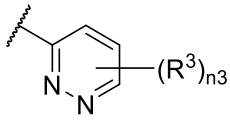
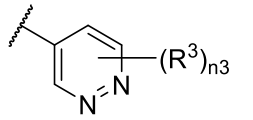
[56] t is 0, 1 or 2.

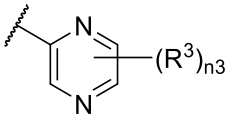
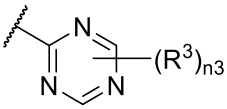
[57] In one ~~embodiment~~example of the compound of formula (IVA), C is 5- to 10-membered heteroaryl or aryl. In some ~~embodiment~~examples, C is 5- to 7-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from O, S, or N as a ring member. In some ~~embodiment~~examples, C, which is substituted with (R^3)n3, is pyrazole, imidazole, oxazole, oxadiazole, oxazolone, isoxazole, thiazole, pyridyl, pyrazine, furan or pyrimidyl. In some ~~embodiment~~examples, C, which is substituted with (R^3)n3, is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , .

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,

 , or  , wherein R^{3a} is C_1-C_3 alkyl.

[58] In one ~~embodiment~~example of the compound of formula (IVA), R^1 and R^2 are each independently Cl, -CN, $-CF_3$, -OH, methyl, methoxy, or $–CONH_2$.

[59] In one ~~embodiment~~example of the compound of formula (IVA),

[60] A and B are phenyl;

[61] X is $-(CR^5R^6)_t-$;

[62] Y and Z are each -O-;

[63] V is $-CH_2-$ or $-CH_2CH_2-$;

[64] L is halogen;

[65] R^1 and R^2 are each independently hydrogen, halogen, -CN, $-CF_3$, -OH, or optionally substituted C_1-C_6 alkyl;

[66] R^5 and R^6 are each independently hydrogen, halogen, -OH, or C_1-C_3 alkyl; and

[67] R^{16} is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl.

[68] In one ~~embodiment~~example of the compound of formula (IVA),

[69] A and B are phenyl;

[70] X is $-(CR^5R^6)_t-$;

[71] W is $-CH_2-$ or $-C(CH_3)H-$;

[72] Y and Z are each -O-;

[73] V is $-CH_2CH_2-$;

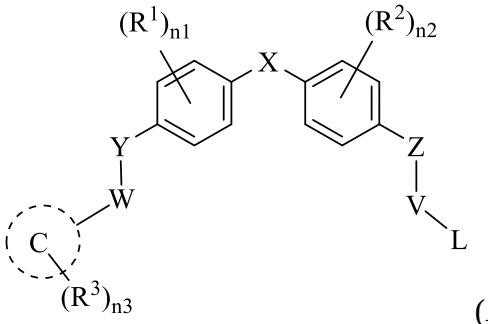
[74] L is halogen;

[75] R^1 and R^2 are each independently hydrogen, halogen, or –CN;

[76] R^5 and R^6 are each independently hydrogen, or C_1-C_3 alkyl; and

[77] R^{16} is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl.

[78] In one ~~embodiment~~example, the present disclosure provides compounds comprising the structure of formula (A-I):



(A-I),

[79] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[80] C is a phenyl or a 5- to 7-membered monocyclic heteroaryl comprising 1, 2, or 3 heteroatoms selected from O, S, or N as a ring member;

[81] X is a bond, $-(CR^5R^6)_t-$, or $-NR^7-$;

[82] Y is a bond, $-CH_2-$, $-C(CH_3)H-$, -O-, -S-, -NH-, $-NCH_3-$, or $-N(COCH_3)-$;

[83] Z is a bond, $-CH_2-$, -O-, or -NH-;

[84] W is a bond, $-CH_2-$, $-C(CH_3)H-$, -C(=O)-, $-N(R^7)CO-$, or $-CONR^7-$;

[85] V is $-CH_2-$ and L is halogen, $-NH_2$, or $-CF_3$; or

[86] V is $-CH_2CH_2-$ and L is halogen or $-NH_2$;

[87] R^1 and R^2 are each independently hydrogen, halogen, -CN, $-CF_3$, methyl, or $-CONH_2$;

[88] R^3 is selected from from -CN, C_1-C_3 alkoxy, $-CF_3$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, $-S(C_1$-C_3 alkyl), $-SO_2(C_1$-C_3 alkyl), $-NH_2$, $-(C_1$-C_3 alkyl)NH_2, $-NHSO_2CH_3$, $-NHSO_2CF_3$, $-N(CH_3)SO_2CH_3$, $-NHSO_2CH_2CH_3$, $-N(CH_3)SO_2CH_2CH_3$, $-CH_2NHSO_2CH_3$, $-CH_2N(CH_3)SO_2CH_3$, $-SO_2NH_2$, $-CONH_2$, $-CON(C_1$-C_3 alkyl$)_2$, $-CONH(C_1$-C_3 alkyl), $-NHCO(C_1$-C_3 alkyl), $-N(CH_3)COO(C_1$-C_3 alkyl), $-NHCO(C_1$-C_3 alkyl), or $-N(CH_3)COO(C_1$-C_3 alkyl);

[89] R^5 and R^6 are each independently hydrogen, halogen, -OH, or C_1-C_3 alkyl;

[90] R^7 is H or C_1-C_6 alkyl;

[91] n1 and n2 are each independently 0, 1, or 2;

[92] n3 is 1, 2, 3, 4 or 5; and

[93] t is 0, 1 or 2.

[94] In one ~~embodiment~~example of the compound of formula (IVA),

[95] In one ~~embodiment~~example of the compound of formula (A-I), at least one R^3 is selected from -CN, C_1-C_3 alkoxy, -$CONH_2$, -$NHSO_2CH_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, or -SO_2CH_3 and the other R^3, if present, is selected from -CN, -CF_3, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, -S(C_1-C_3 alkyl), -SO_2(C_1-C_3 alkyl), -NH_2, -(C_1-C_3 alkyl)NH_2, -$NHSO_2CH_3$, -$NHSO_2CF_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, -$CH_2NHSO_2CH_3$, -$CH_2N(CH_3)SO_2CH_3$, -SO_2NH_2, -$CONH_2$, -CON(C_1-C_3 alkyl)$_2$, -CONH(C_1-C_3 alkyl), -NHCO(C_1-C_3 alkyl), -$N(CH_3)$COO(C_1-C_3 alkyl), -NHCO(C_1-C_3 alkyl), or -$N(CH_3)$COO(C_1-C_3 alkyl).

[96] In one ~~embodiment~~example of the compound of formula (A-I),

[97] X is a bond or -$(CR^5R^6)_t$;

[98] W is a bond, -CH_2-, or -$C(CH_3)H$-;

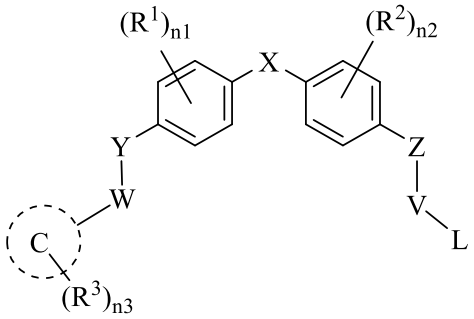
[99] Y is -O-;

[100] Z is -O-;

[101] V is -CH_2- or -CH_2CH_2-; and

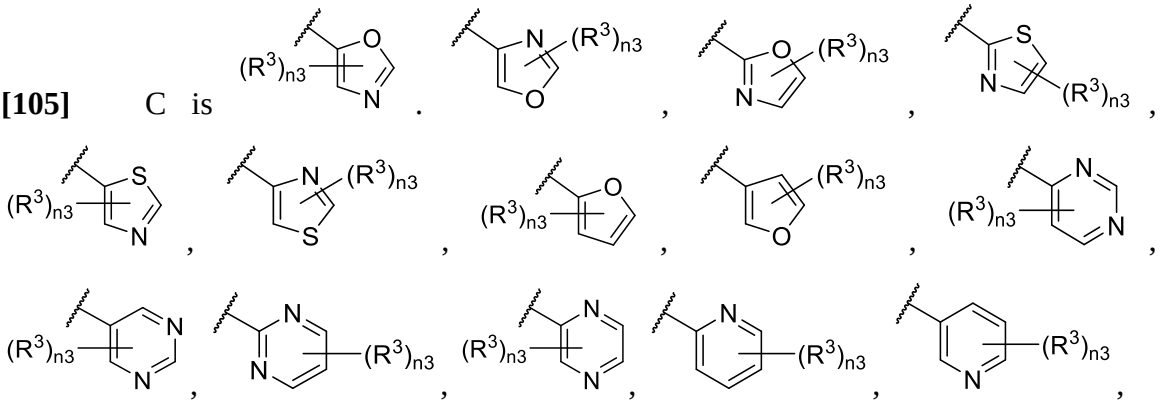
[102] L is halogen

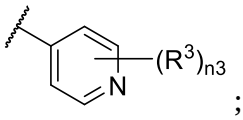
[103] In one ~~embodiment~~example, the present disclosure provides compounds comprising the structure of formula (G-II):



(G-II),

[104] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[105] C is 

or  ;

[106] X is -$(CR^5R^6)_t$-;

[107] Y is -O-;

[108] Z is -O-;

[109] W is -CH_2- or -$C(CH_3)H$-;

[110] V is -CH_2CH_2-;

[111] L is halogen;

[112] R^1 and R^2 are each independently Cl or -CN;

[113] at least one R^3 is selected from -CN, C_1-C_3 alkoxy, -$CONH_2$, -$NHSO_2CH_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, or -SO_2CH_3 and the other R^3, if present, is selected from -CN, -CF_3, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, -S(C_1-C_3 alkyl), -SO_2(C_1-C_3 alkyl), -NH_2, -(C_1-C_3 alkyl)NH_2, -$NHSO_2CH_3$, -$NHSO_2CF_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, -$CH_2NHSO_2CH_3$, -$CH_2N(CH_3)SO_2CH_3$, -SO_2NH_2, -$CONH_2$, -$CON(C_1$-C_3 alkyl$)_2$, -$CONH(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), -$N(CH_3)COO(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), or -$N(CH_3)COO(C_1$-C_3 alkyl);

[114] R^5 and R^6 are each independently hydrogen or methyl;

[115] n1 and n2 are each independently 0, 1, or 2;

[116] n3 is 1 or 2; and

[117] t is 1.

[118] In one ~~embodiment~~example of the compound of formula (G-II), at least one R^3 is selected from -$NHSO_2CH_3$, -$NHSO_2CH_2CH_3$, or -SO_2CH_3 and the other R^3, if present, is selected from -CN, C_1-C_3 alkyl, C_1-C_3 alkoxy, -SO_2(C_1-C_3 alkyl), -NH_2, -(C_1-C_3 alkyl)NH_2, -$NHSO_2CH_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, -SO_2NH_2, -$CONH_2$, -$CON(C_1$-C_3 alkyl$)_2$, -$CONH(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), -$N(CH_3)COO(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), or -$N(CH_3)COO(C_1$-C_3 alkyl).

[119] In one ~~embodiment~~example, the present disclosure provides Compounds A1-A96, A98-A116, A118-A159, A161-A175, and A177-A234, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof. In one ~~embodiment~~example, the present disclosure provides Compounds A13, A57, A74, A93, A109, A112, A122, A126, A131, A134, A136, A137, A164, A168, A169, A170, A171, A172, A184, A185, A195, and/or A204, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof.

[120] In one ~~embodiment~~example, the present disclosure provides a pharmaceutical composition comprising any one of the compound of formula (IIIA), or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a pharmaceutically acceptable carrier. In one ~~embodiment~~example, the present disclosure provides a pharmaceutical composition comprising any one of the compound of formula (IVA), or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a pharmaceutically acceptable carrier. In one ~~embodiment~~example, the present disclosure provides a pharmaceutical composition comprising any one of the compound of formula (A-I), or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a pharmaceutically acceptable carrier. In one ~~embodiment~~example, the present disclosure provides a pharmaceutical composition comprising any one of the compound of formula (G-II), or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a pharmaceutically acceptable carrier.

[121] In one ~~embodiment~~example, the present disclosure provides a pharmaceutical composition comprising any one of Compounds A1-A96, A98-A116, A118-A159, A161-A175, and A177-A234, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a pharmaceutically acceptable carrier. In one ~~embodiment~~example, the present disclosure provides a pharmaceutical composition comprising any one of Compounds A13, A57, A74, A93, A109, A112, A122, A126, A131, A134, A136, A137, A164, A168, A169, A170, A171, A172, A184, A185, A195, and A204, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a pharmaceutically acceptable carrier.

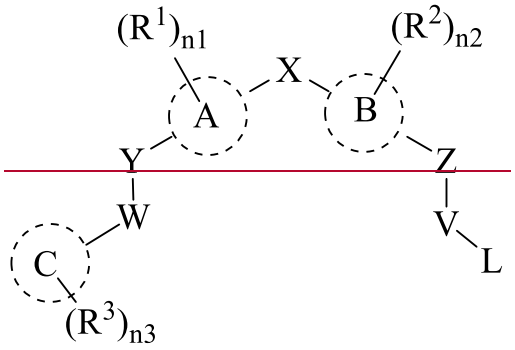
[122] In one ~~embodiment~~example, the present disclosure provides a method for treating cancer, comprising administering any one of the compound of formula (IIIA), (IVA), (A-I), or (G-II), and Compounds A1-A96, A98-A116, A118-A159, A161-A175, or A177-A234, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, to a subject in need thereof. In one ~~embodiment~~example, the cancer is prostate cancer. In one ~~embodiment~~example, the prostate cancer is metastatic castration-resistant prostate cancer. In other ~~embodiment~~examples, the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant.

[123] In one ~~embodiment~~example, the present disclosure provides a method for treating cancer, comprising administering any one of Compounds A13, A57, A74, A93, A109, A112, A122, A126, A131, A134, A136, A137, A164, A168, A169, A170, A171, A172, A184, A185, A195, and A204, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

WHAT IS CLAIMED IS:

1. A compound having the structure of formula (IIIA):



(IIIA)

or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

A and B are each independently selected from phenyl, pyridyl, pyrimidyl, or thiophene;

C is a 3- to 10-membered ring;

X is a bond, $-(CR^5R^6)_t-$, or $-NR^7-$;

Y is a bond, $-(CR^8R^9)_m-$, $-O-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-NR^7-$, or $-N(COCH_3)-$;

W is a bond, $-(CR^{8a}R^{9a})_m-$, $-C(=O)-$, $-N(R^7)CO-$, $-CONR^7-$, or $-NSO_2R^7-$;

Z is a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$;

V is $-CH_2-$ and L is halogen, $-NH_2$, $-CHCl_2$, $-CCl_3$, or $-CF_3$; or

V is $-CH_2CH_2-$ and L is halogen or $-NH_2$;

R^1 and R^2 are each independently hydrogen, halogen, $-CN$, $-CF_3$, $-OH$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted $-(C_1$-C_6 alkyl)-(C_1-C_6 alkoxy), optionally substituted $-(C_1$-C_6 alkyl)-OH, $-NR^{13}R^{14}$, optionally substituted $-(C_1$-C_6 alkyl)-$NR^{13}R^{14}$, $-NR^{14}SO_2R^{16}$, optionally substituted $-(C_1$-C_6 alkyl)$NR^{14}SO_2R^{16}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_1$-C_6 alkyl)-$NR^{14}COR^{16}$, $-CONR^{13}R^{14}$, optionally substituted $-(C_1$-C_6 alkyl)-$CONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-(C_1$-C_6 alkyl)-$SO_2NR^{14}R^{15}$, optionally substituted $-SO_2R^{16}$ or optionally substituted $-(C_1$-C_6 alkyl)-SO_2R^{16};

R^3 is selected from halogen, oxo, =S, $=NR^{16}$, $-CN$, $-CF_3$, $-OH$, $-S(C_1$-C_3 alkyl), C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-NR^{13}R^{14}$, $-(C_1$-C_3 alkyl)-$NR^{13}R^{14}$, $-NR^{14}SO_2R^{16}$, $-(C_1$-C_3 alkyl)$NR^{14}SO_2R^{16}$, $-NR^{14}COR^{16}$, $-(C_1$-C_6 alkyl)-$NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, $-(C_1$-C_3 alkyl)-

~~$CONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-(C_1-C_3\text{ alkyl})-SO_2NR^{14}R^{15}$, $-SO_2(C_1-C_3\text{ alkyl})$, or $-(C_1-C_6\text{ alkyl})-SO_2(C_1-C_3\text{ alkyl})$;~~

~~R^5 and R^6 are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or C_1-C_3 alkoxy; or R^5 and R^6 taken together form an optionally substituted 3- to 6-membered carbocyclyl or heterocyclyl;~~

~~R^7 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;~~

~~R^8 and R^9 are each independently hydrogen, halogen, or C_1-C_3 alkyl;~~

~~R^{8a} and R^{9a} are each independently hydrogen, $-OH$, halogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-NR^{13}R^{14}$, $-(C_1-C_3\text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3\text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_3\text{ alkyl})-CONR^{14}R^{15}$; or R^{8a} and R^{8b} taken together form an optionally substituted 3- to 6-membered carbocyclyl or heterocyclyl;~~

~~R^{13}, R^{14} and R^{15} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form a 3- to 6-membered heterocyclyl;~~

~~R^{16} is hydrogen, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, C_3-C_6 cycloalky, or phenyl;~~

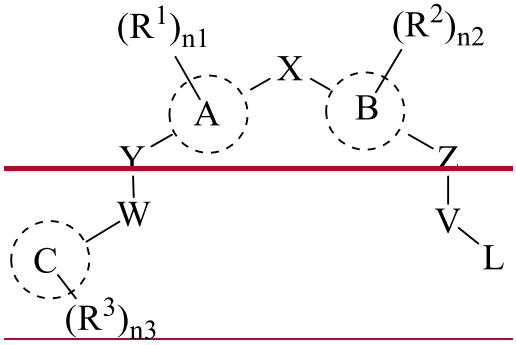
~~each m is independently 0, 1, or 2;~~

~~n1 and n2 are each independently 0, 1, or 2;~~

~~n3 is 1, 2, 3, 4 or 5; and~~

~~t is 0, 1 or 2.~~

~~2. The compound of claim 1, wherein the compound has the structure of formula (IVA):~~



~~(IVA)~~

~~or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:~~

~~A and B are each independently selected from phenyl, pyridyl, pyrimidyl, or thiophene;~~

~~C is a 3- to 10-membered ring;~~

X is a bond, -$(CR^5R^6)_t$-, or -NR^7-;

Y and Z are each independently a bond, -CH_2-, -$C(CH_3)H$-, -O-, -S-, -NH-, -NCH_3-, or -$N(COCH_3)$-;

W is a bond, -CH_2-, -$C(CH_3)H$-, -C(=O)-, -$N(R^7)CO$-, or -$CONR^7$-;

V is -CH_2- and L is halogen, -NH_2, or -CF_3; or

V is -CH_2CH_2- and L is halogen or -NH_2;

R^1 and R^2 are each independently hydrogen, halogen, -CN, -CF_3, -OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted -(C_1-C_6 alkyl)-(C_1-C_6 alkoxy), optionally substituted -(C_1-C_6 alkyl)-OH, -$NR^{13}R^{14}$, optionally substituted -(C_1-C_6 alkyl)-$NR^{13}R^{14}$, -$NR^{14}SO_2R^{16}$, optionally substituted -(C_1-C_6 alkyl)$NR^{14}SO_2R^{16}$, -$NR^{14}COR^{16}$, optionally substituted -(C_1-C_6 alkyl)-$NR^{14}COR^{16}$, -$CONR^{13}R^{14}$, optionally substituted -(C_1-C_6 alkyl)-$CONR^{14}R^{15}$, -$SO_2NR^{14}R^{15}$, optionally substituted -(C_1-C_6 alkyl)-$SO_2NR^{14}R^{15}$, optionally substituted -SO_2R^{16}, optionally substituted -(C_1-C_6 alkyl)-SO_2R^{16};

R^3 is selected from halogen, oxo, =S, $=NR^{16}$, -CN, -CF_3, -OH, -S(C_1-C_3 alkyl), C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, -$NR^{13}R^{14}$, -(C_1-C_3 alkyl)-$NR^{13}R^{14}$, -$NR^{14}SO_2R^{16}$, -(C_1-C_3 alkyl)$NR^{14}SO_2R^{16}$, -$NR^{14}COR^{16}$, -(C_1-C_6 alkyl)-$NR^{14}COR^{16}$, -$CONR^{14}R^{15}$, -(C_1-C_3 alkyl)-$CONR^{14}R^{15}$, -$SO_2NR^{14}R^{15}$, -(C_1-C_3 alkyl)-$SO_2NR^{14}R^{15}$, -SO_2(C_1-C_3 alkyl), or -(C_1-C_6 alkyl)-SO_2(C_1-C_3 alkyl);

R^5 and R^6 are each independently hydrogen, halogen, -OH, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or C_1-C_3 alkoxy; or R^5 and R^6 taken together form an optionally substituted 3- to 6-membered carbocyclyl or heterocyclyl;

R^7 is H or C_1-C_6 alkyl;

R^{13}, R^{14} and R^{15} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form a 3- to 6-membered heterocyclyl;

R^{16} is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl;

n1 and n2 are each independently 0, 1, or 2;

n3 is 1, 2, 3, 4 or 5; and

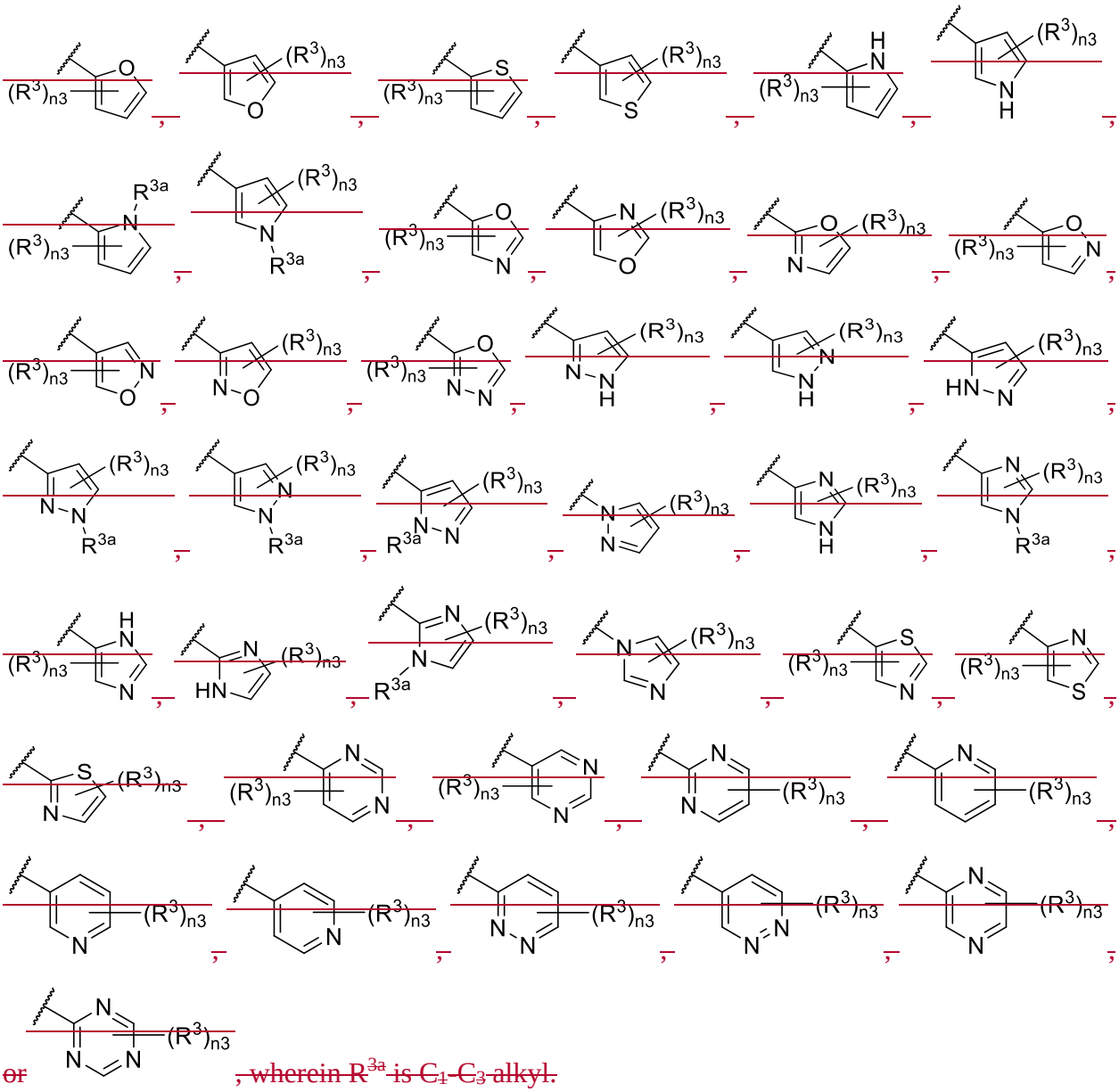
t is 0, 1 or 2.

3. The compound of claim 2, wherein C is 5- to 10-membered heteroaryl or aryl.

4. The compound of claim 3, wherein C is 5- to 7-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from O, S, or N as a ring member.

5. The compound of claim4, wherein C, which is substituted with $(R^3)_{n3}$, is pyrazole, imidazole, oxazole, oxadiazole, oxazolone, isoxazole, thiazole, pyridyl, pyrazine, furan or pyrimidyl.

6. The compound of claim 5, wherein C, which is substituted with $(R^3)_{n3}$, is selected from



or , wherein R^{3a} is C_1-C_3 alkyl.

~~7. The compound of claim 6, wherein R^1 and R^2 are each independently Cl, -CN, $-CF_3$, -OH, methyl, methoxy, or $-CONH_2$.~~

~~8. The compound of claim 2, wherein:~~

~~A and B are phenyl;~~

~~X is $-(CR^5R^6)_t-$;~~

~~Y and Z are each -O-;~~

~~V is $-CH_2-$ or $-CH_2CH_2-$;~~

~~L is halogen;~~

~~R^1 and R^2 are each independently hydrogen, halogen, -CN, $-CF_3$, -OH, or optionally substituted C_1-C_6 alkyl;~~

~~R^5 and R^6 are each independently hydrogen, halogen, -OH, or C_1-C_3 alkyl; and~~

~~R^{16} is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl.~~

~~9. The compound of claim 8, wherein:~~

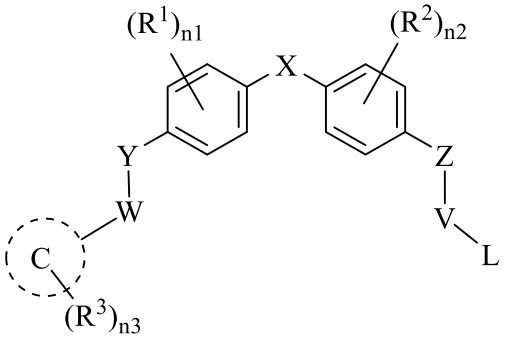
~~R^5 and R^6 are each independently hydrogen, or C_1-C_3 alkyl;~~

~~W is $-CH_2-$ or $-C(CH_3)H-$;~~

~~V is $-CH_2CH_2-$; and~~

~~R^1 and R^2 are each independently hydrogen, halogen, or -CN.~~

~~10~~1. ~~The compound of claim 1, wherein the~~A compound ~~has~~ having the structure of formula (A-I)~~:~~



(A-I)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer ~~or prodrug~~ thereof, wherein:

C is a 5- to 7-membered monocyclic heteroaryl comprising 1, 2, or 3 heteroatoms selected from O, S, or N as a ring member;

X is a bond, -$(CR^5R^6)_t$-, or -NR^7;

Y is a bond, -CH_2-, -$C(CH_3)H$-, -O-, -S-, -NH-, -NCH_3-, or –$N(COCH_3)$-;

Z is a bond, -CH_2-, -O-, or -NH-;

W is a bond, -CH_2-, -$C(CH_3)H$-, -C(=O)-, -$N(R^7)CO$-, or -$CONR^7$-;

V is -CH_2- and L is halogen, -NH_2, or -CF_3; or

V is -CH_2CH_2- and L is halogen or -NH_2;

R^1 and R^2 are each independently hydrogen, halogen, -CN, -CF_3, methyl, or –$CONH_2$;

R^3 is selected from -CN, C_1-C_3 alkoxy, -CF_3, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, -$S(C_1$-C_3 alkyl), -$SO_2(C_1$-C_3 alkyl), -NH_2, -$(C_1$-C_3 alkyl)NH_2, -$NHSO_2CH_3$, -$NHSO_2CF_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, -$CH_2NHSO_2CH_3$, -$CH_2N(CH_3)SO_2CH_3$, -SO_2NH_2, -$CONH_2$, -$CON(C_1$-C_3 alkyl)$_2$, -$CONH(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), -$N(CH_3)COO(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), or -$N(CH_3)COO(C_1$-C_3 alkyl);

R^5 and R^6 are each independently hydrogen, halogen, -OH, or C_1-C_3 alkyl;

R^7 is H or C_1-C_6 alkyl;

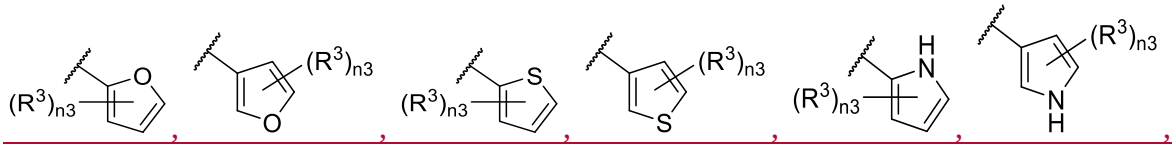
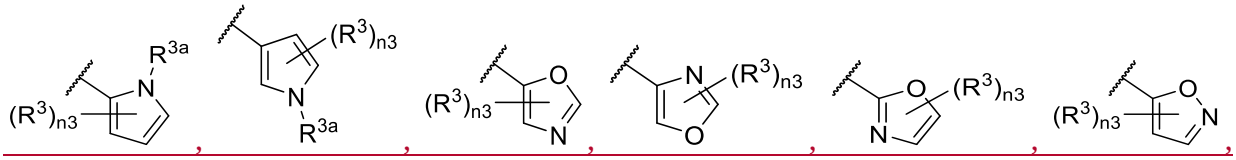
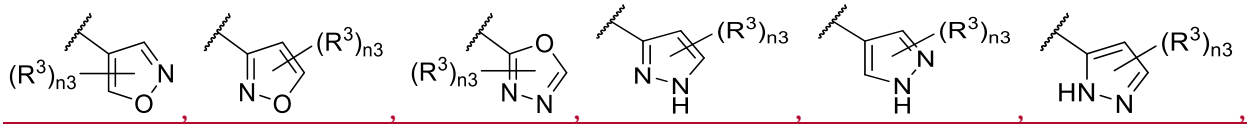
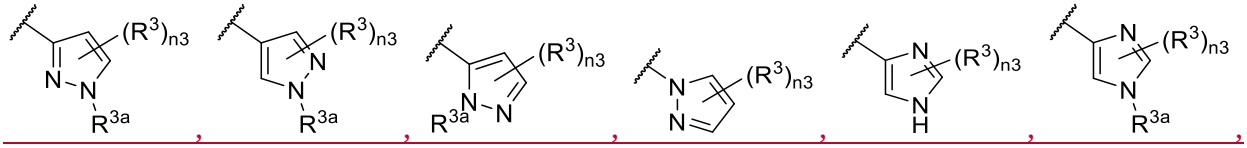
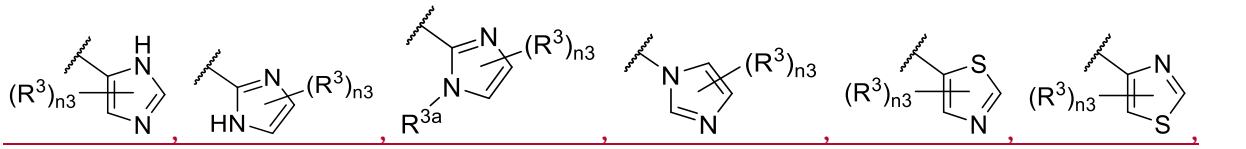
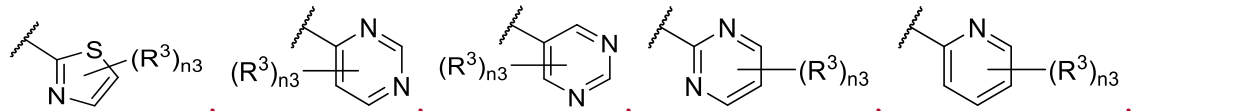
n1 and n2 are each independently 0, 1, or 2;

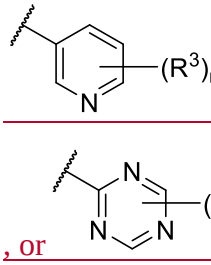
n3 is 1, 2, 3, 4 or 5; and

t is 0, 1 or 2.

2. The compound of claim 1, wherein C, which is substituted with (R^3)n3, is pyrazole, imidazole, oxazole, oxadiazole, oxazolone, isoxazole, thiazole, pyridyl, pyrazine, furan or pyrimidyl.

3. The compound of claim 2, wherein C, which is substituted with (R^3)n3, is selected from



, or , wherein R^{3a} is C_1-C_3 alkyl.

4. The compound of claim 1, wherein:

X is $-(CR^5R^6)_t-$;

Y and Z are each -O-;

V is $-CH_2-$ or $-CH_2CH_2-$; and

L is halogen.

5. The compound of claim 4, wherein:

R^5 and R^6 are each independently hydrogen, or C_1-C_3 alkyl;

W is -CH_2- or -$C(CH_3)H$-;

V is -CH_2CH_2-; and

R^1 and R^2 are each independently hydrogen, halogen, or –CN.

~~11~~6. The compound of claim 1~~10~~, wherein:

at least one R^3 is selected from -CN, C_1-C_3 alkoxy, -$CONH_2$, -$NHSO_2CH_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, or -SO_2CH_3 and the other R^3, if present, is selected from -CN, -CF_3, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, -S(C_1-C_3 alkyl), -SO_2(C_1-C_3 alkyl), -NH_2, -(C_1-C_3 alkyl)NH_2, -$NHSO_2CH_3$, -$NHSO_2CF_3$, -$N(CH_3)SO_2CH_3$, -$NHSO_2CH_2CH_3$, -$N(CH_3)SO_2CH_2CH_3$, -$CH_2NHSO_2CH_3$, -$CH_2N(CH_3)SO_2CH_3$, -SO_2NH_2, -$CONH_2$, -CON(C_1-C_3 alkyl)$_2$, -CONH(C_1-C_3 alkyl), -NHCO(C_1-C_3 alkyl), -$N(CH_3)$COO(C_1-C_3 alkyl), -NHCO(C_1-C_3 alkyl), or -$N(CH_3)$COO(C_1-C_3 alkyl).

7~~12~~. The compound of claim 1~~10~~, wherein:

X is a bond or -(CR^5R^6)$_t$;

W is a bond, -CH_2-, or -$C(CH_3)H$-;

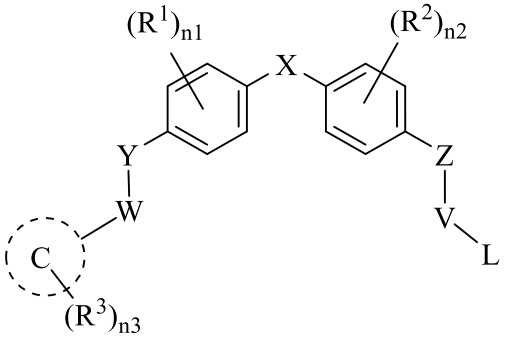
Y is -O-;

Z is -O-;

V is -CH_2- or -CH_2CH_2-; and

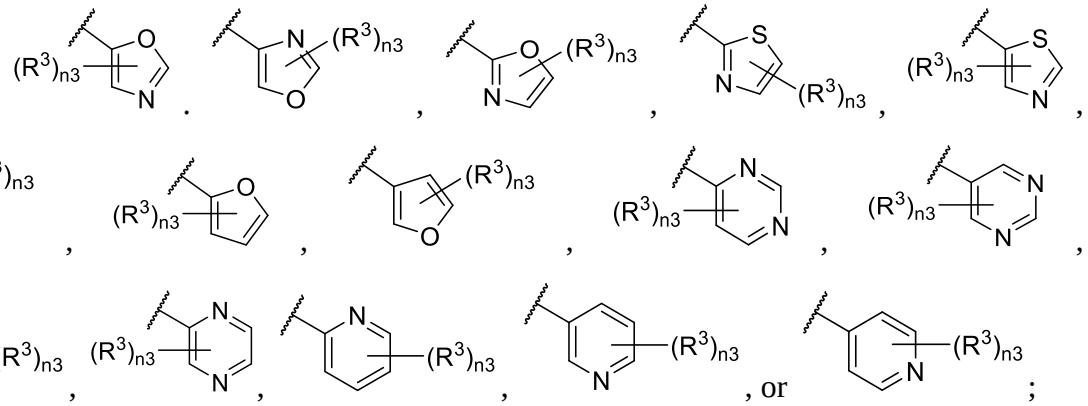
L is halogen.

8~~13~~. The compound of claim 1, wherein the compound has the structure of formula (G-II)



(G-II)

or a pharmaceutically acceptable salt, tautomer, or stereoisomer ~~or prodrug~~ thereof, wherein:

C is  ;

X is $-(CR^5R^6)_t-$;

Y is -O-;

Z is -O-;

W is $-CH_2-$ or $-C(CH_3)H-$;

V is $-CH_2CH_2-$;

L is halogen;

R^1 and R^2 are each independently Cl or -CN;

at least one R^3 is selected from -CN, C_1-C_3 alkoxy, $-CONH_2$, $-NHSO_2CH_3$, $-N(CH_3)SO_2CH_3$, $-NHSO_2CH_2CH_3$, $-N(CH_3)SO_2CH_2CH_3$, or $-SO_2CH_3$ and the other R^3, if present, is selected from -CN, $-CF_3$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, -S(C_1-C_3 alkyl), $-SO_2$(C_1-C_3 alkyl), $-NH_2$, -(C_1-C_3 alkyl)NH_2, $-NHSO_2CH_3$, $-NHSO_2CF_3$, $-N(CH_3)SO_2CH_3$, $-NHSO_2CH_2CH_3$, $-N(CH_3)SO_2CH_2CH_3$, $-CH_2NHSO_2CH_3$, $-CH_2N(CH_3)SO_2CH_3$, $-SO_2NH_2$, $-CONH_2$, -CON(C_1-C_3 alkyl)$_2$, -CONH(C_1-C_3 alkyl), -NHCO(C_1-C_3 alkyl), $-N(CH_3)COO$(C_1-C_3 alkyl), -NHCO(C_1-C_3 alkyl), or $-N(CH_3)COO$(C_1-C_3 alkyl);

R^5 and R^6 are each independently hydrogen or methyl;

n1 and n2 are each independently 0, 1, or 2;

n3 is 1 or 2; and

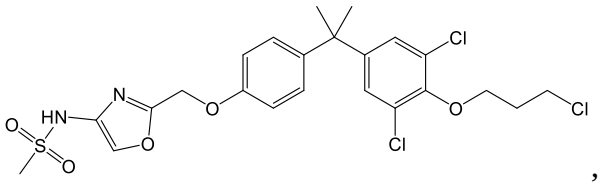
t is 1.

~~9~~14. The compound of claim ~~8~~13, wherein:

at least one R^3 is selected from $-NHSO_2CH_3$, $-NHSO_2CH_2CH_3$, or $-SO_2CH_3$ and the other R^3, if present, is selected from -CN, C_1-C_3 alkyl, C_1-C_3 alkoxy, $-SO_2$(C_1-C_3 alkyl), $-NH_2$, -(C_1-C_3 alkyl)NH_2, $-NHSO_2CH_3$, $-N(CH_3)SO_2CH_3$, $-NHSO_2CH_2CH_3$, $-N(CH_3)SO_2CH_2CH_3$, $-SO_2NH_2$, -

$CONH_2$, -$CON(C_1$-C_3 alkyl$)_2$, -$CONH(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), -$N(CH_3)COO(C_1$-C_3 alkyl), -$NHCO(C_1$-C_3 alkyl), or -$N(CH_3)COO(C_1$-C_3 alkyl).

1015. A compound selected from the group consisting of: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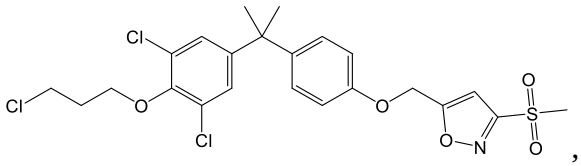
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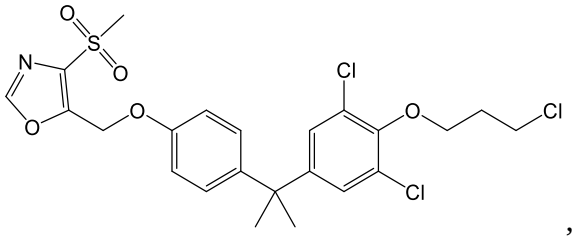
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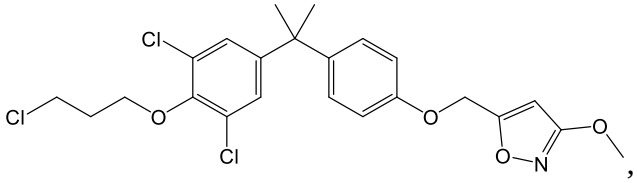
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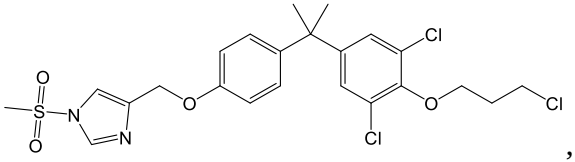
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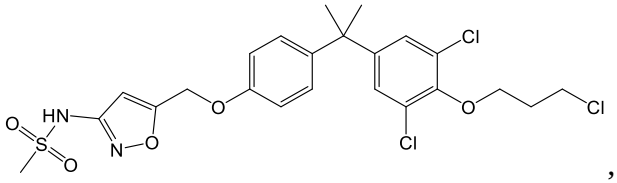
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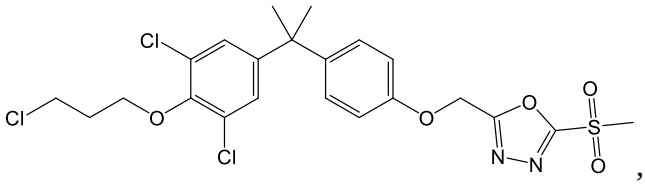
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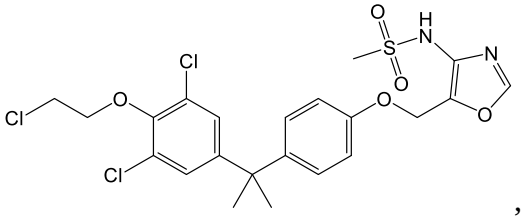
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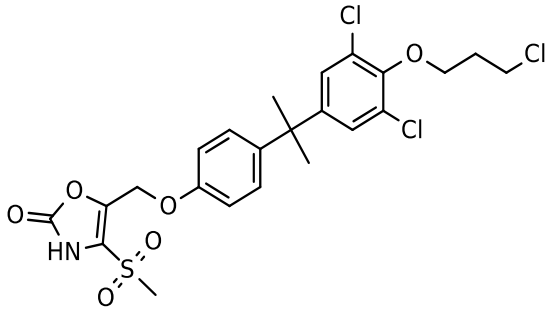
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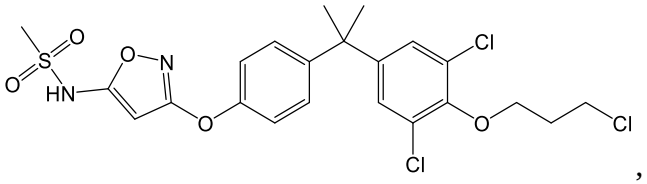
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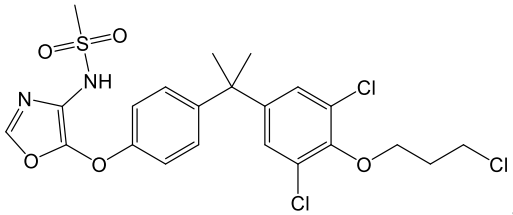
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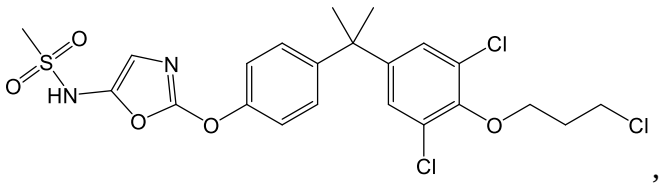
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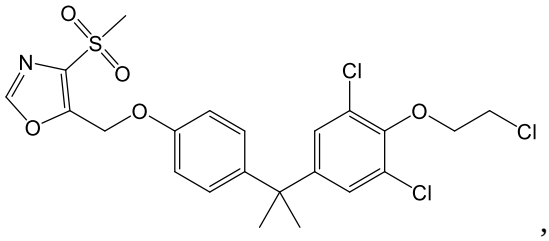
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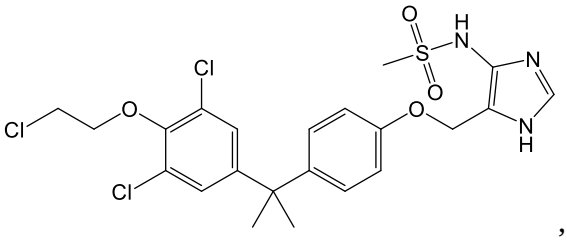
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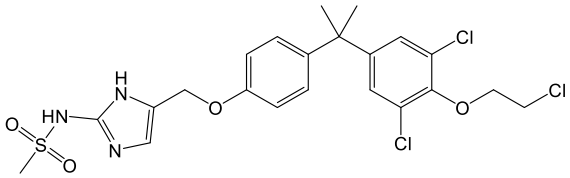
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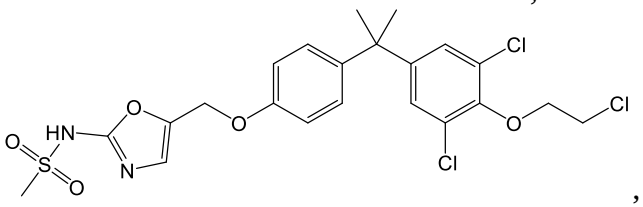
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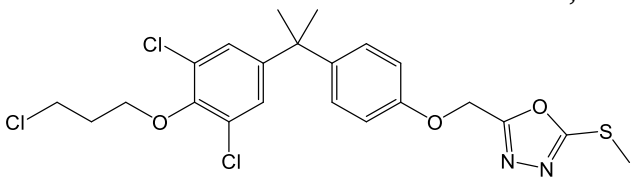
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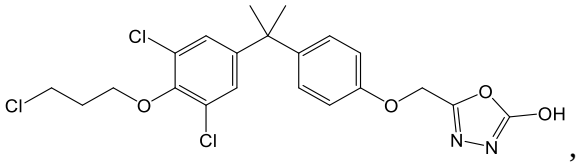
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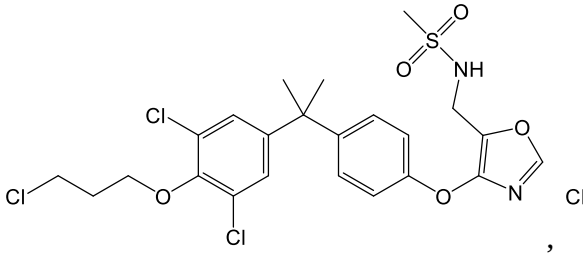
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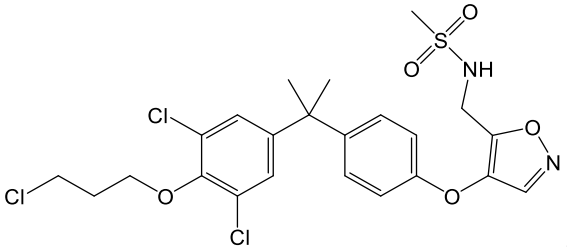
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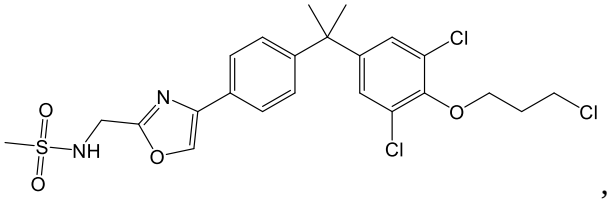
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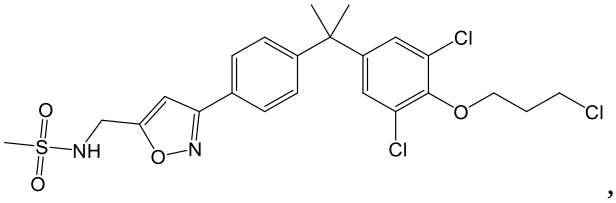
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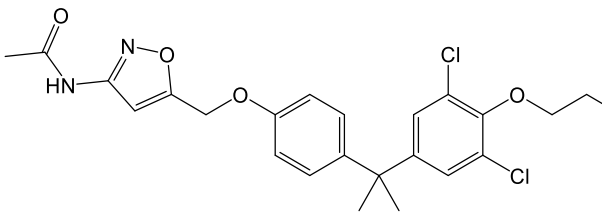
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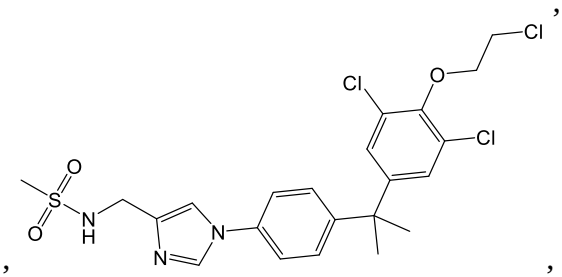
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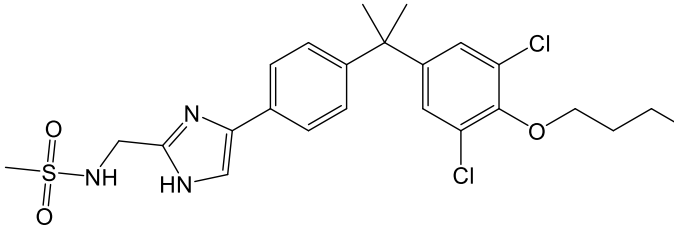
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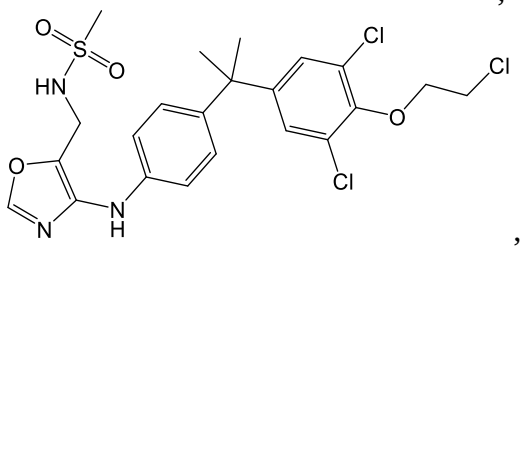
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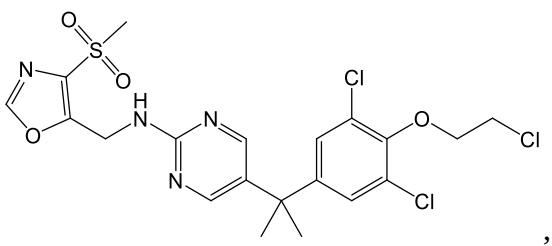
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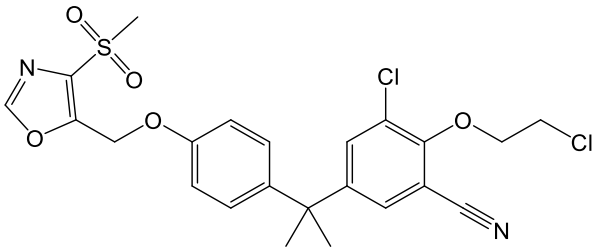
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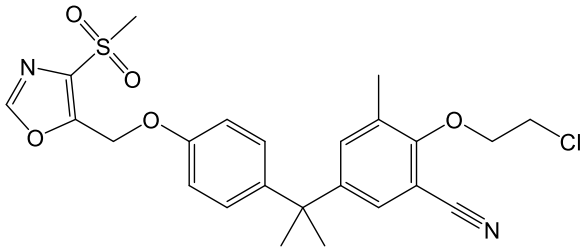
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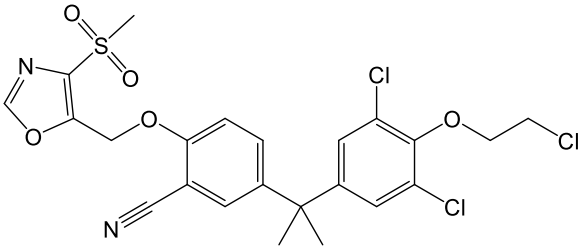
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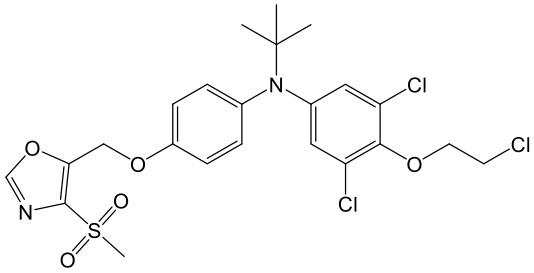
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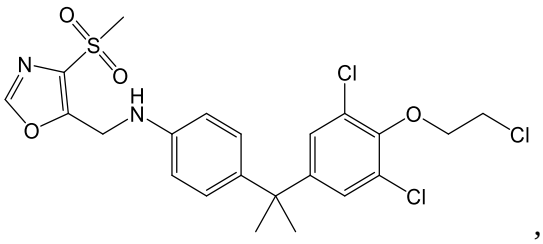
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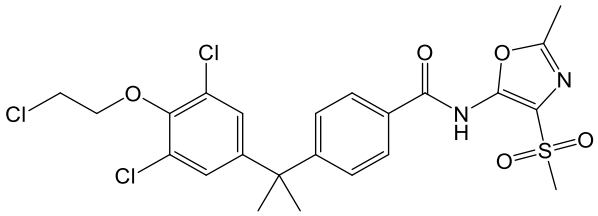
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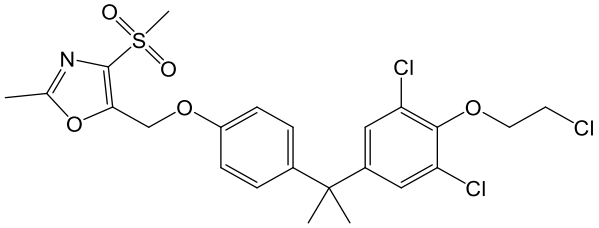
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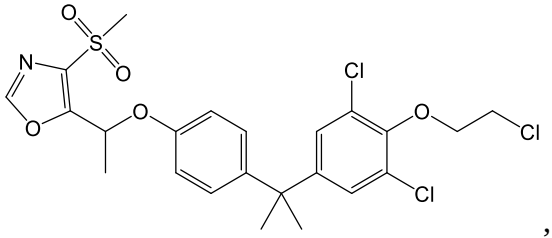
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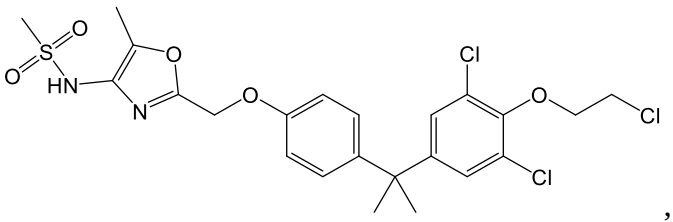
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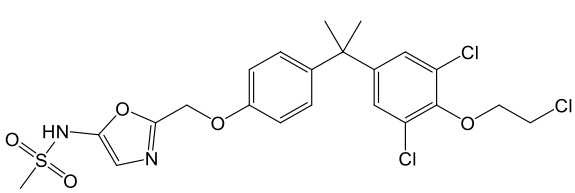
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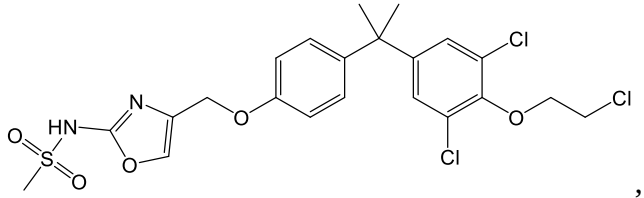
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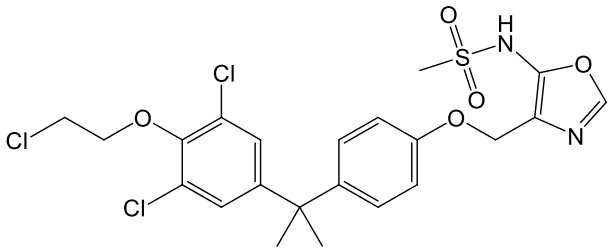
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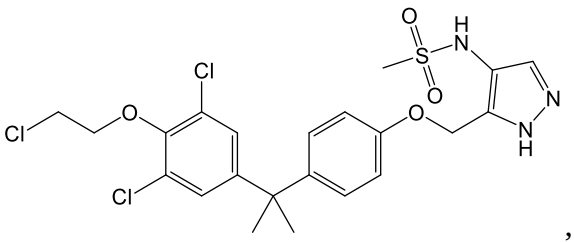
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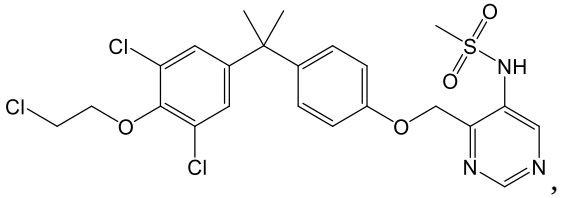
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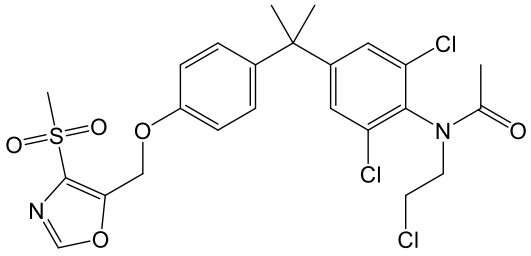
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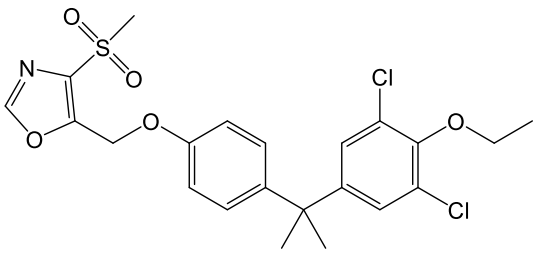
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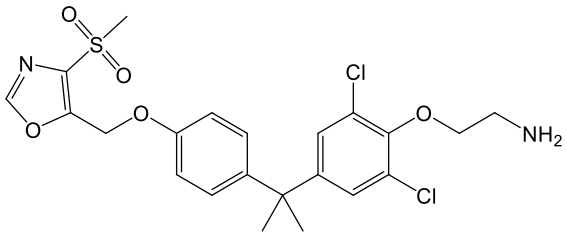
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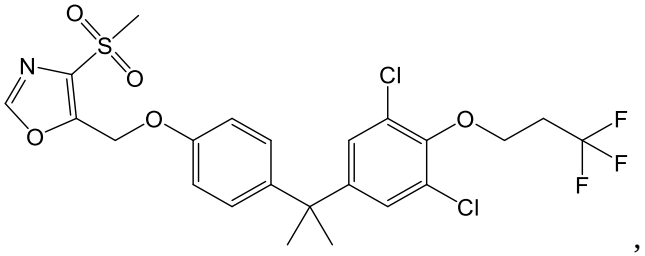
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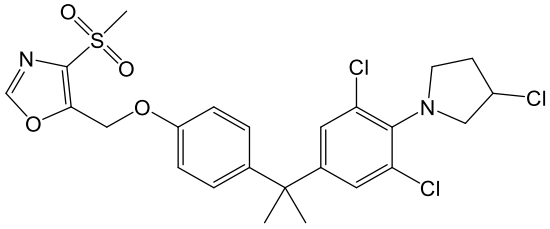
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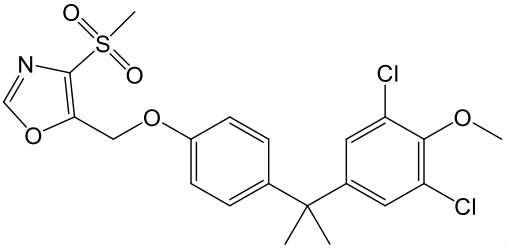
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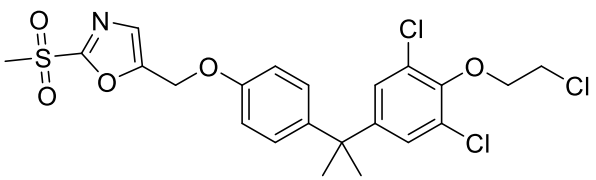
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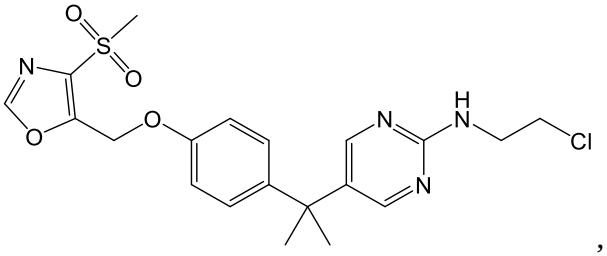
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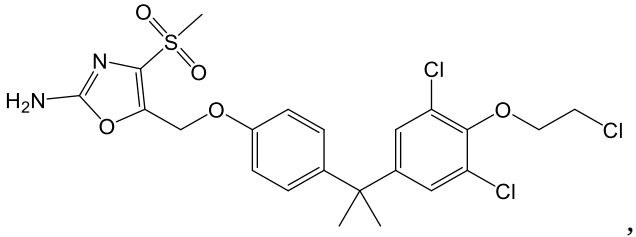
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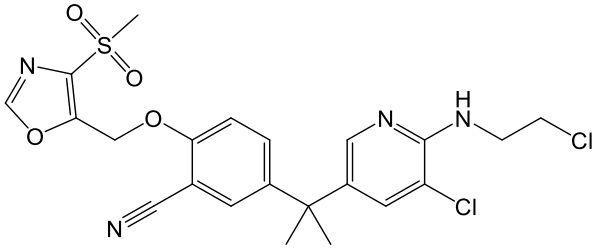
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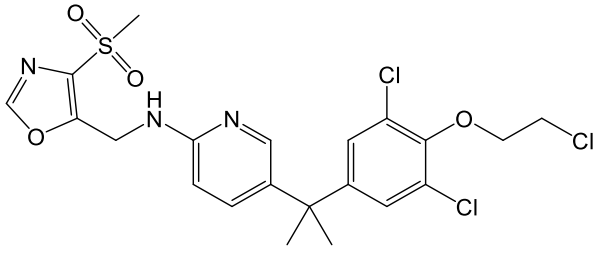
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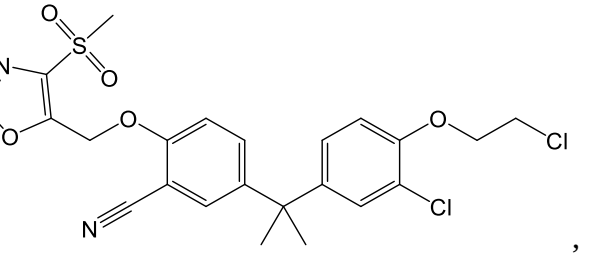
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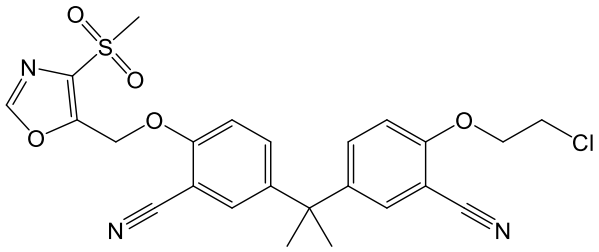
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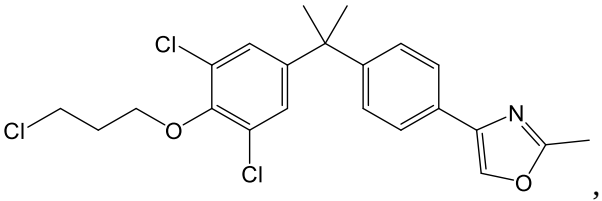
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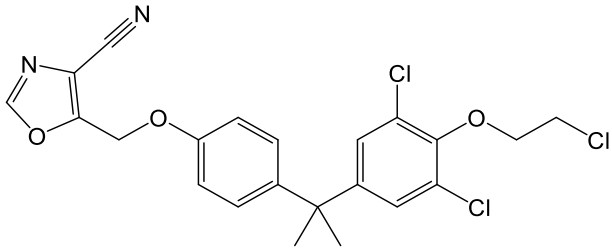
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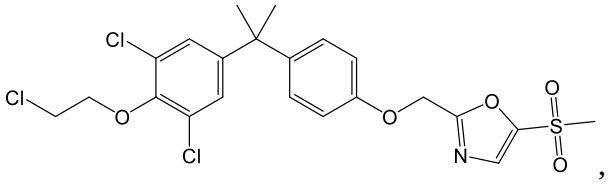
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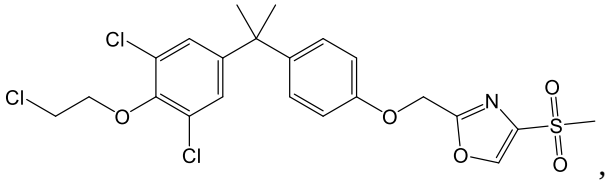
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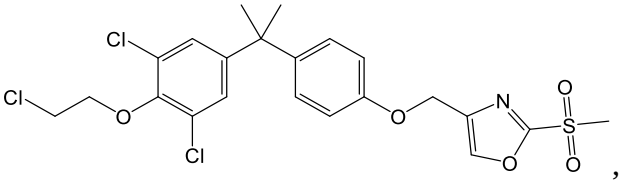
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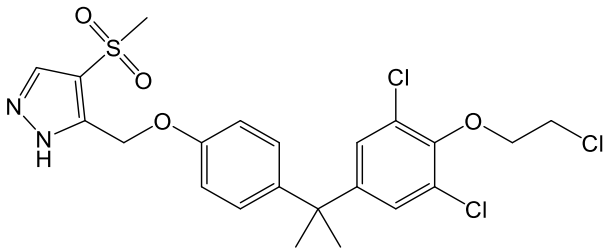
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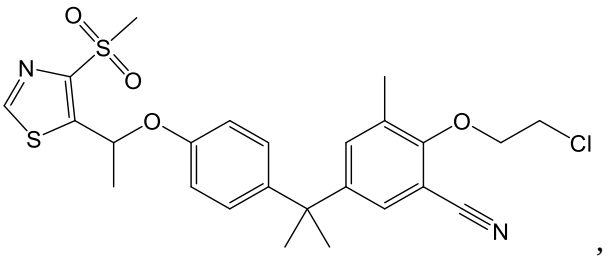
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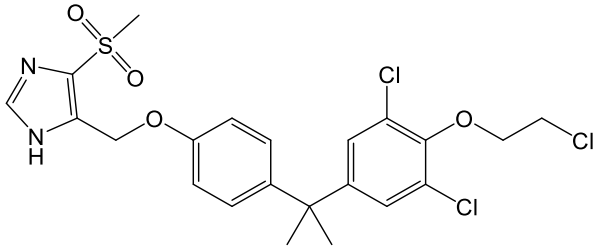
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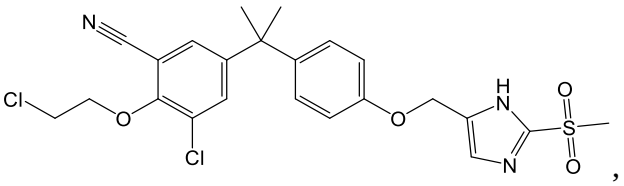
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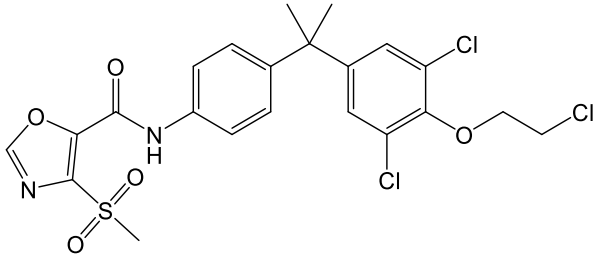
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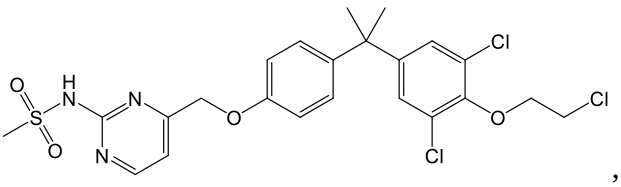
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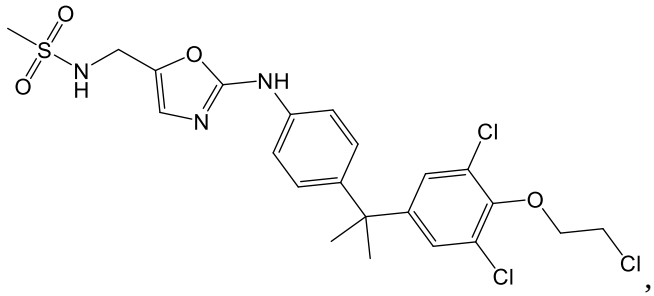
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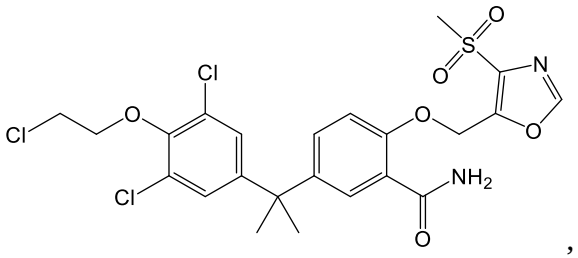
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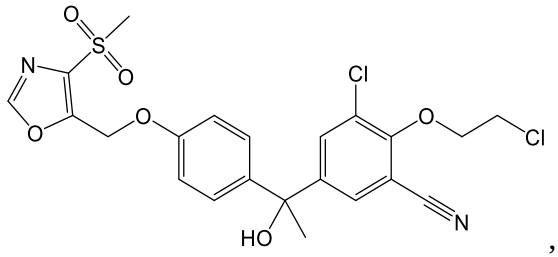
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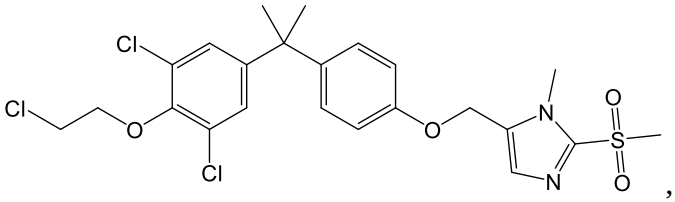
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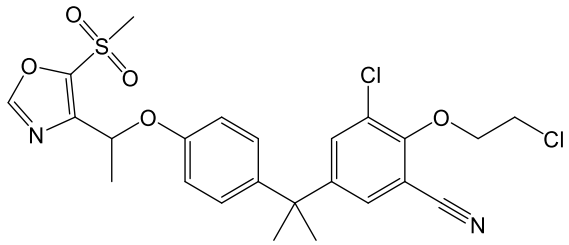
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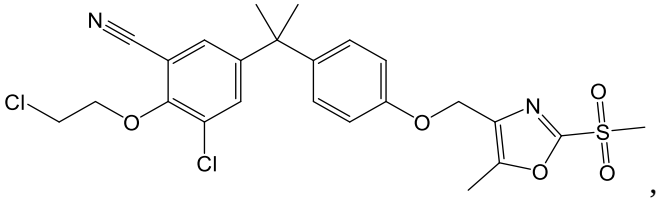
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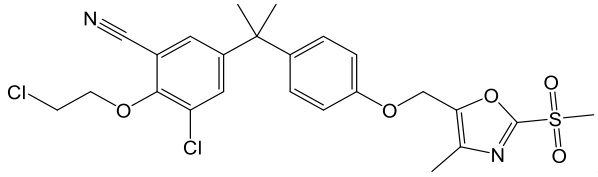
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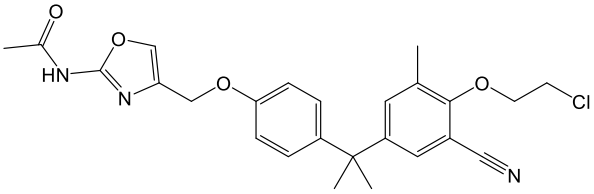
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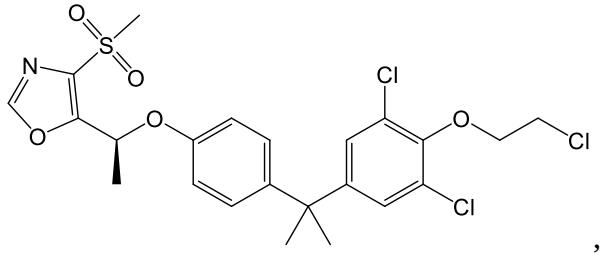
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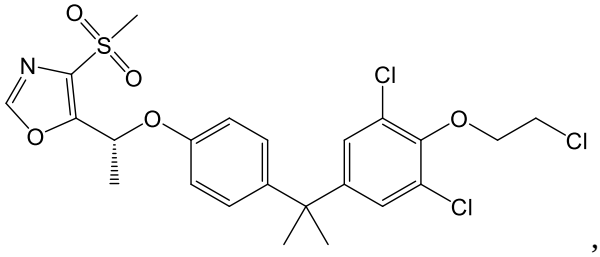
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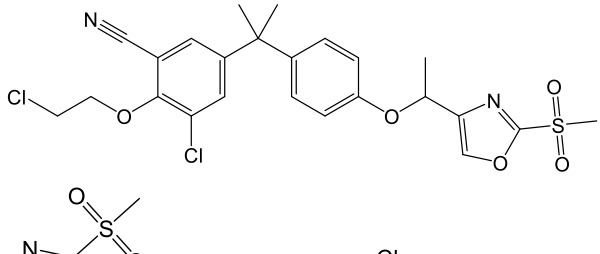
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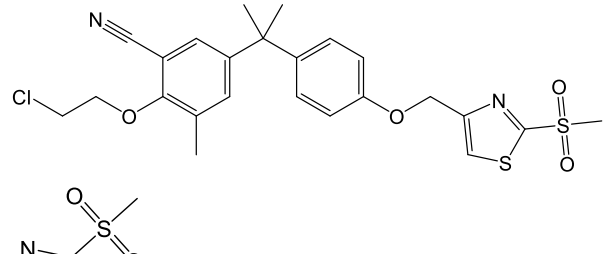
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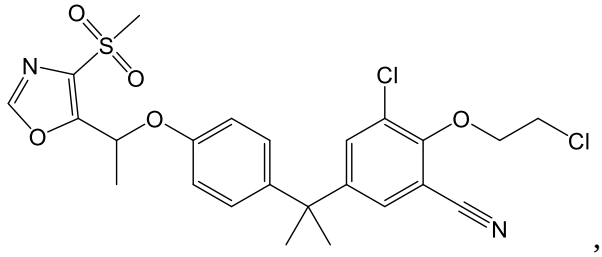
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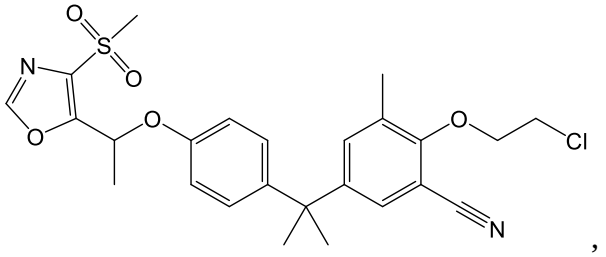
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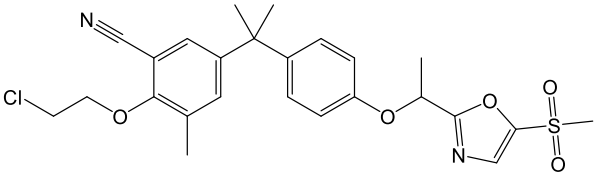
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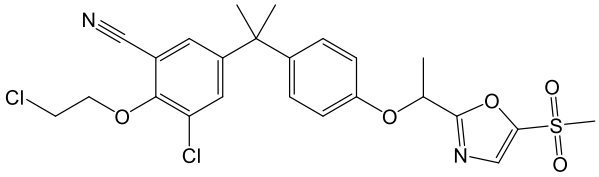
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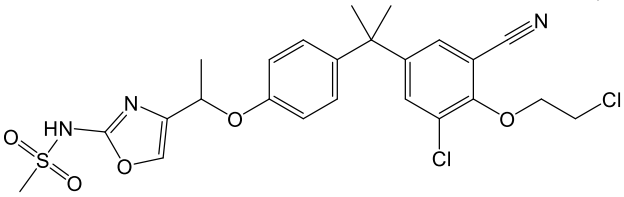
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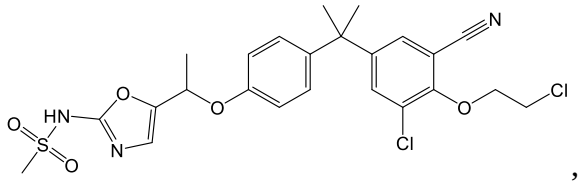
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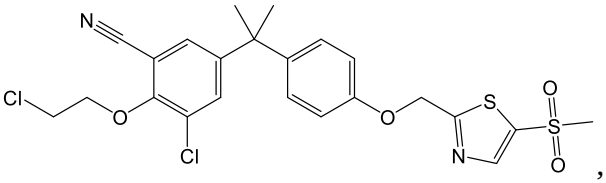
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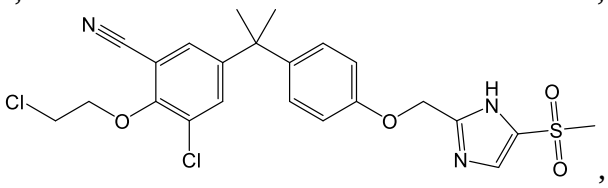
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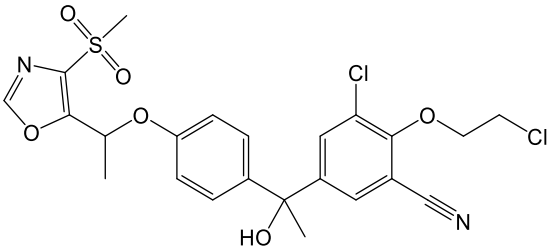
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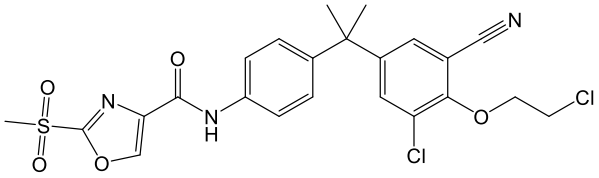
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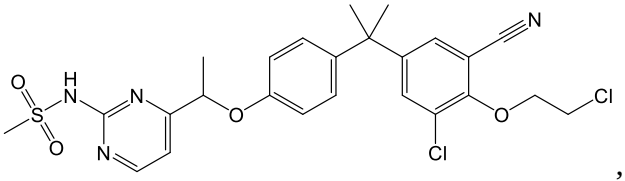
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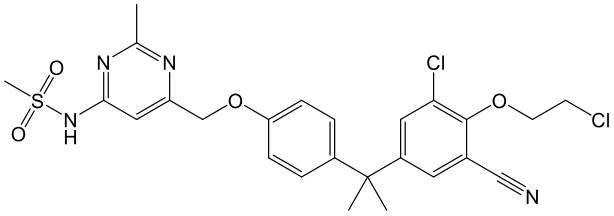
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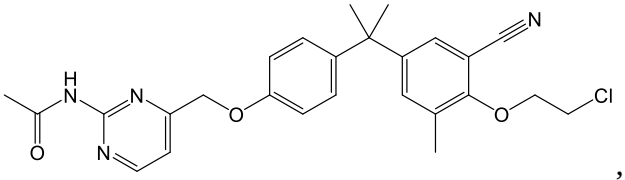
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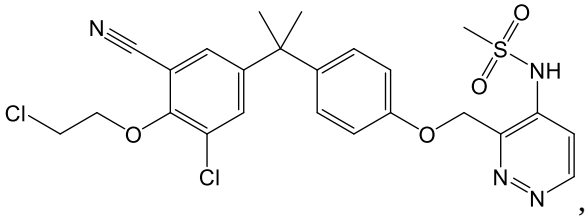
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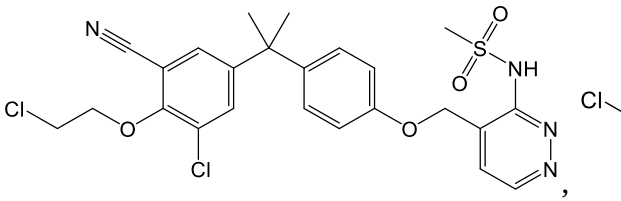
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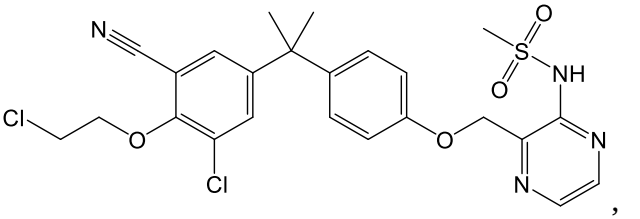
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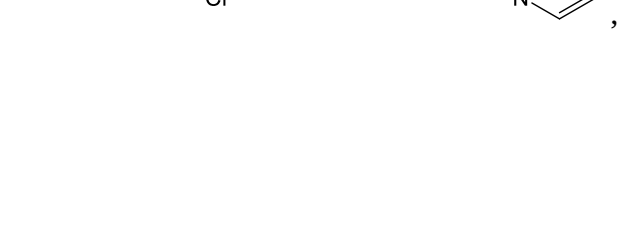
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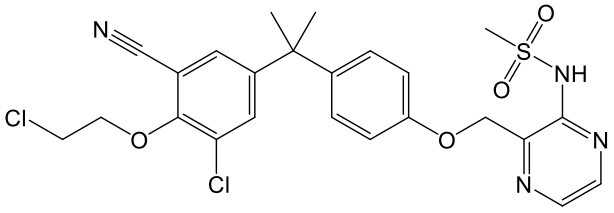
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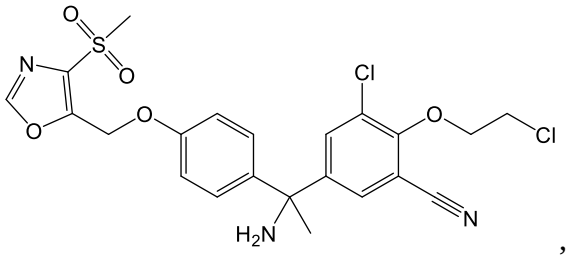
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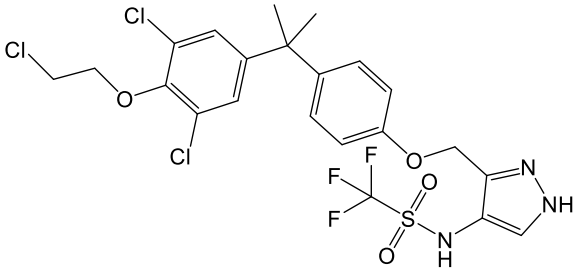
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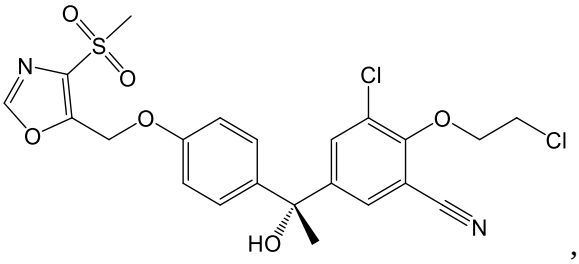
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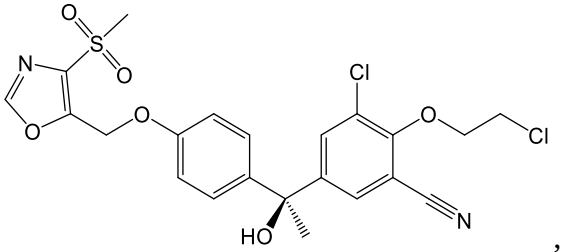
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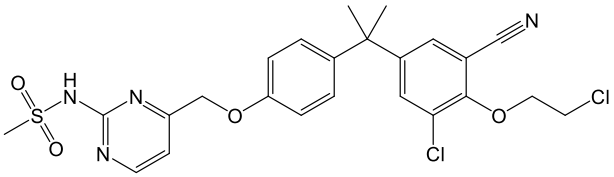
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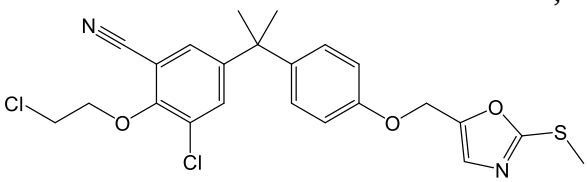
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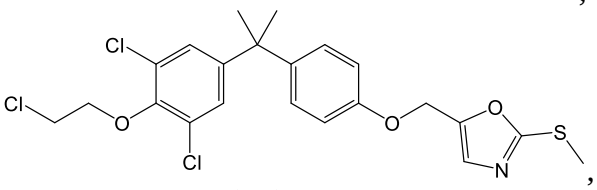
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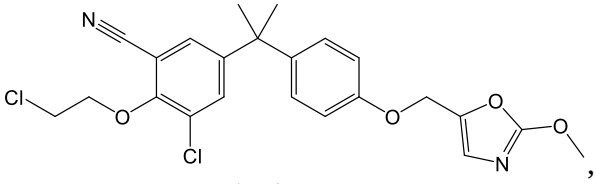
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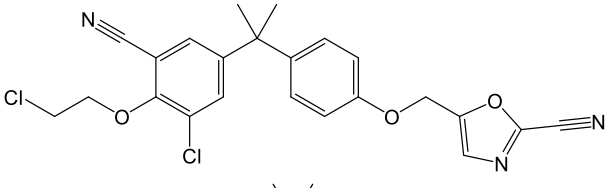
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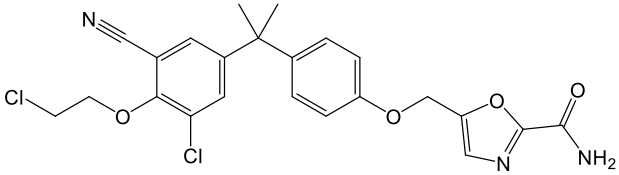
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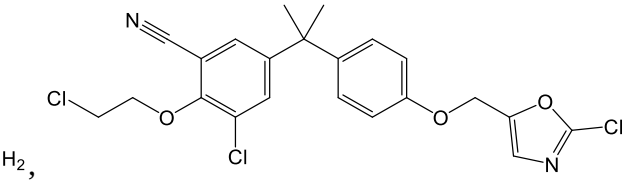
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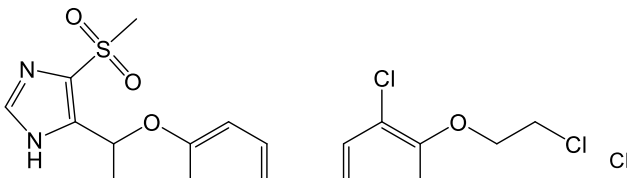
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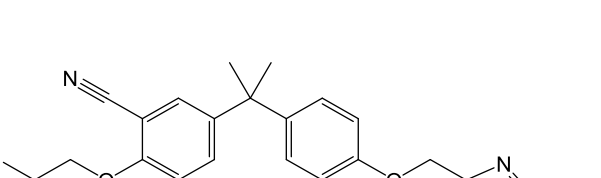
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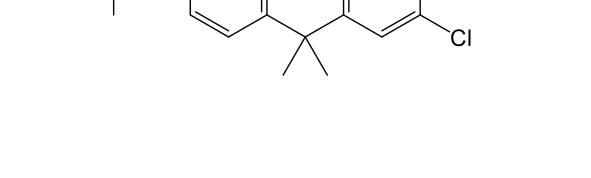
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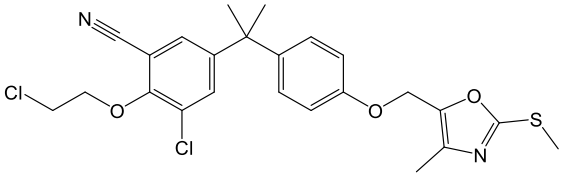
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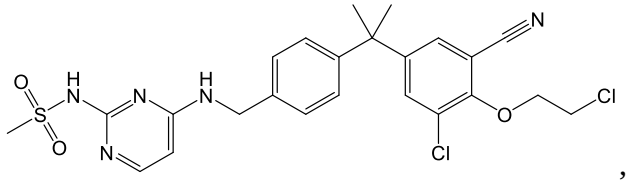
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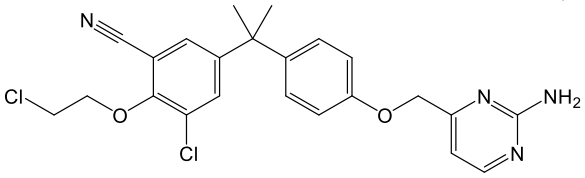
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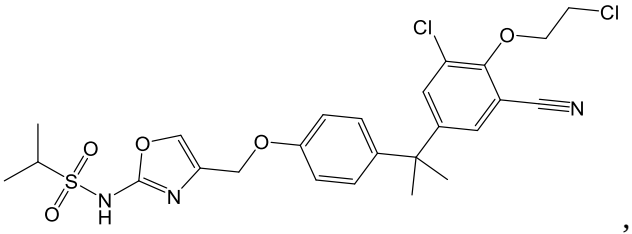
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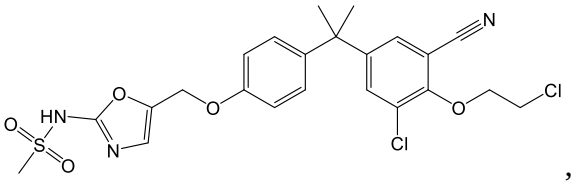
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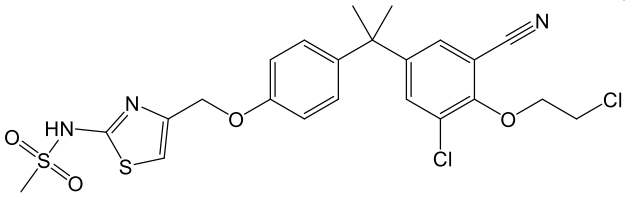
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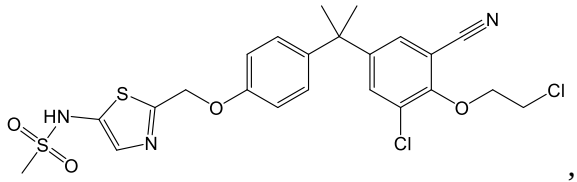
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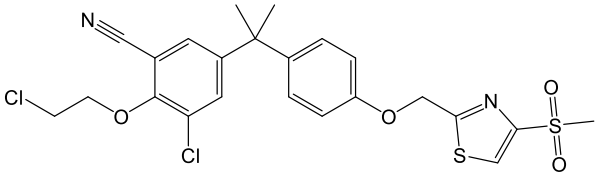
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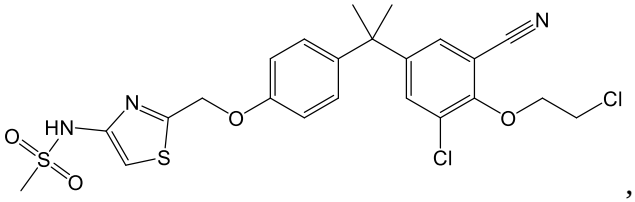
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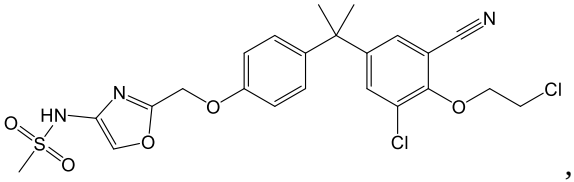
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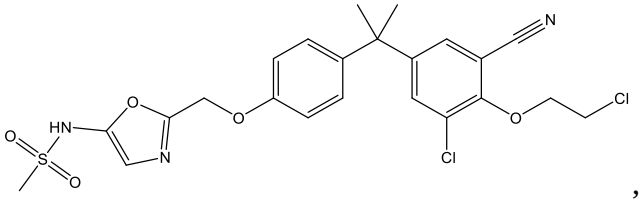
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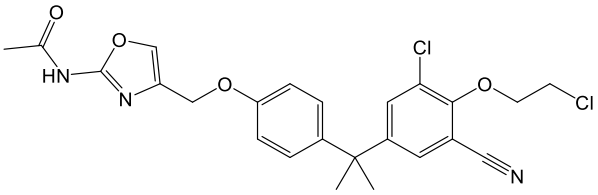
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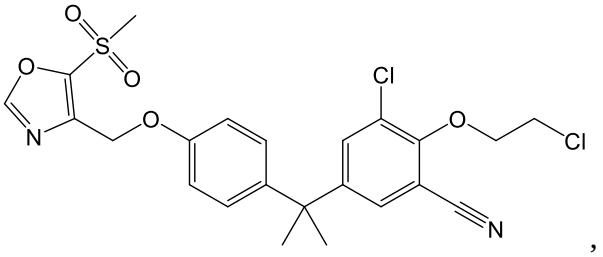
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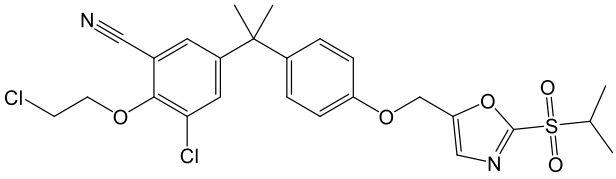
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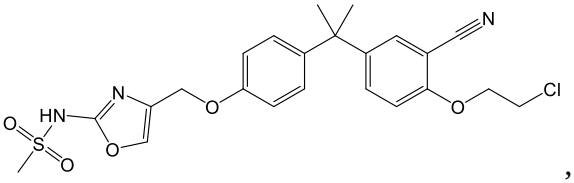
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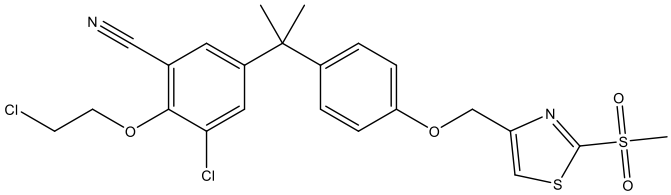
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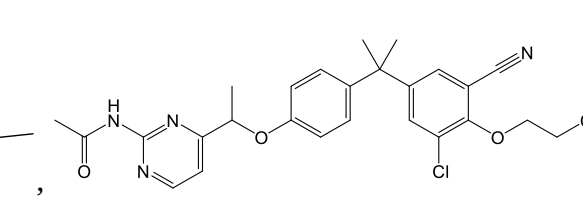
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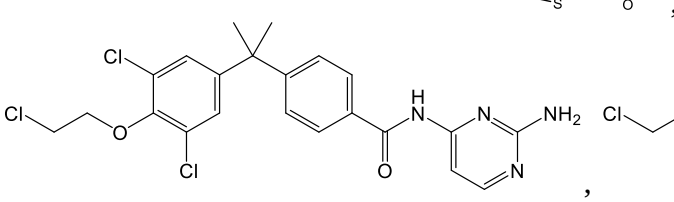
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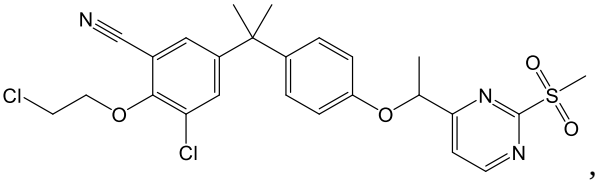
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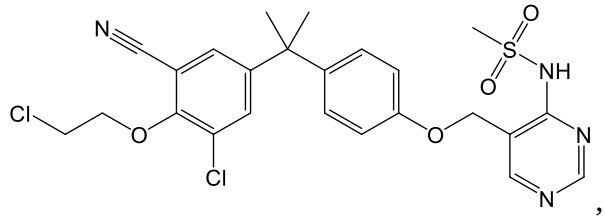
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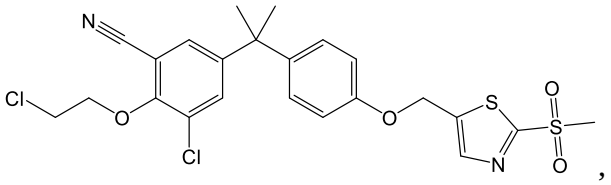
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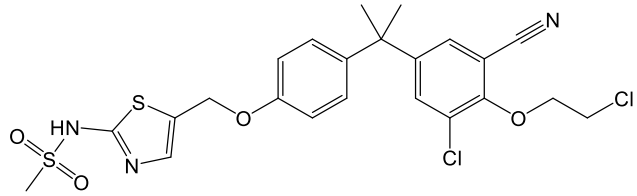
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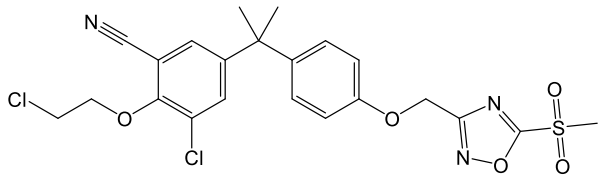
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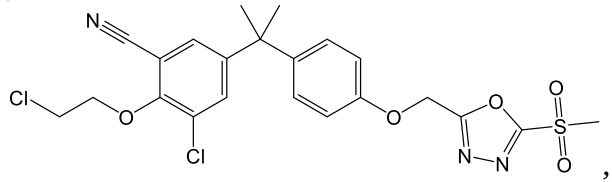
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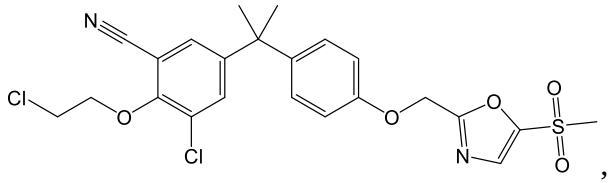
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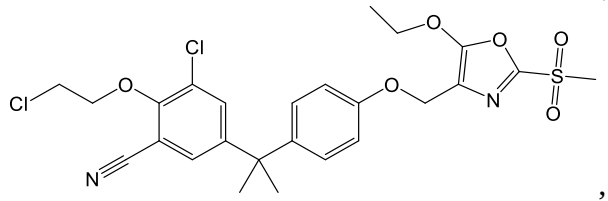
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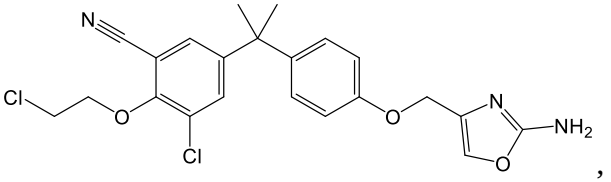
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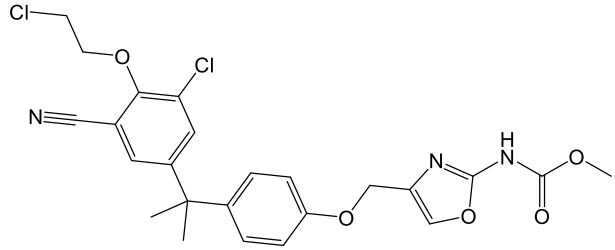
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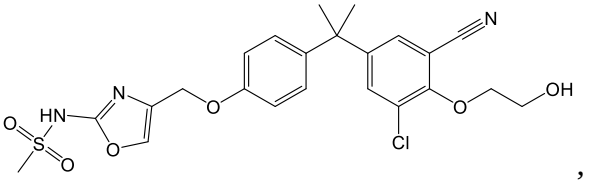
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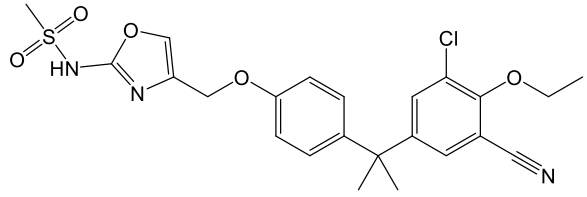
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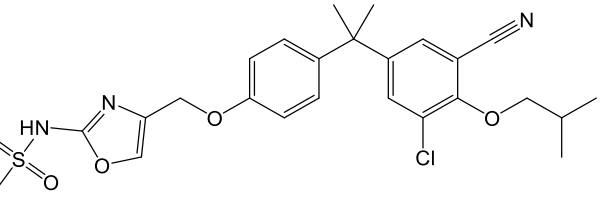
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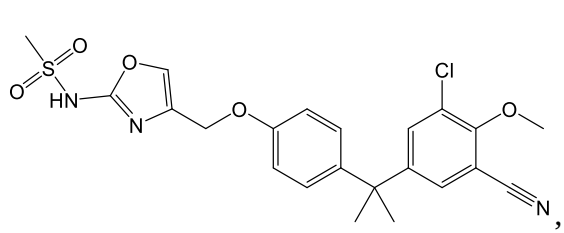
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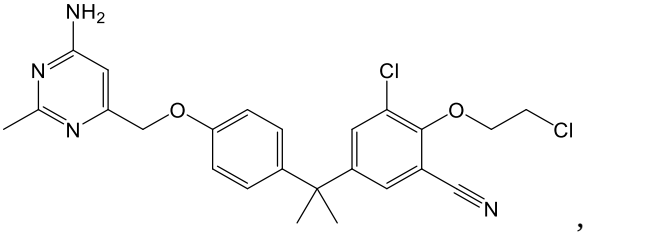
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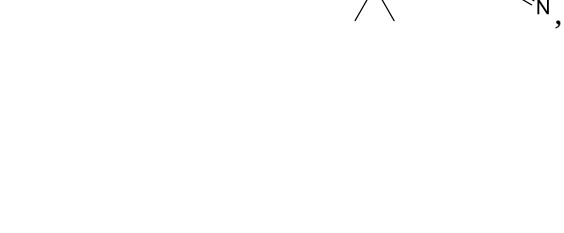
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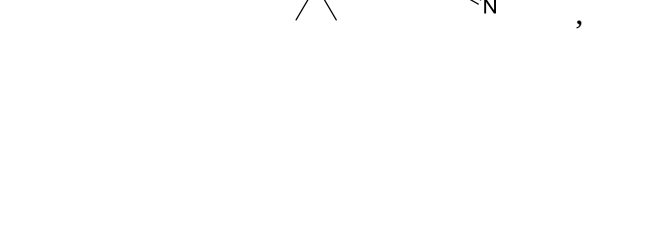
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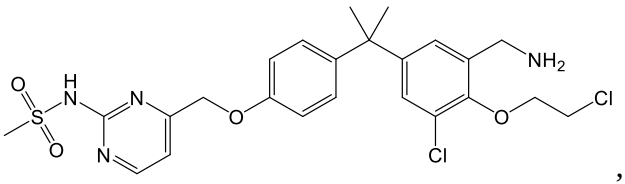
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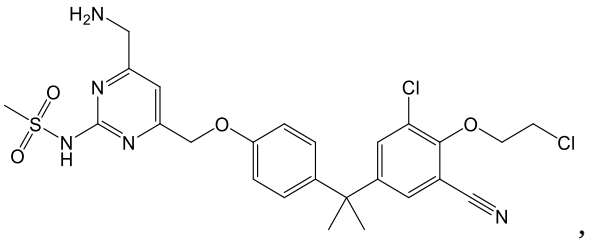
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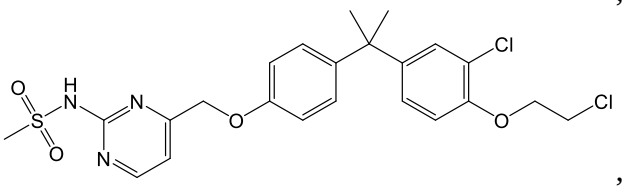
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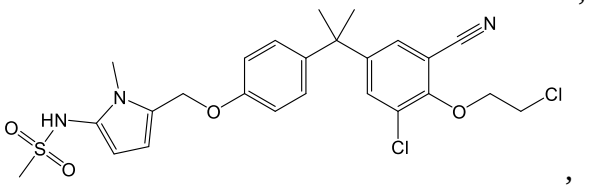
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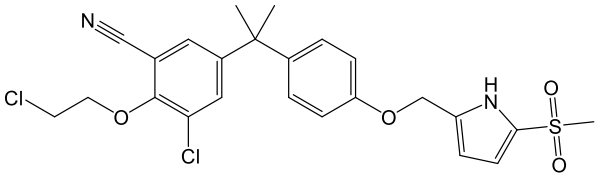
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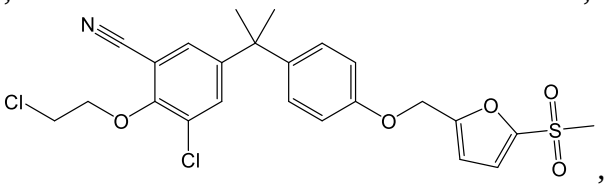
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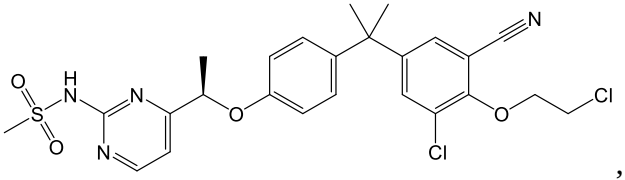
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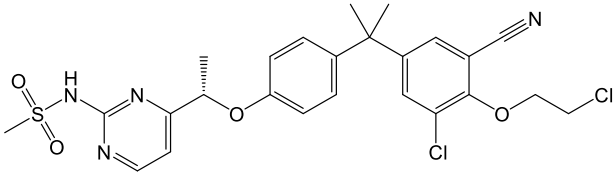
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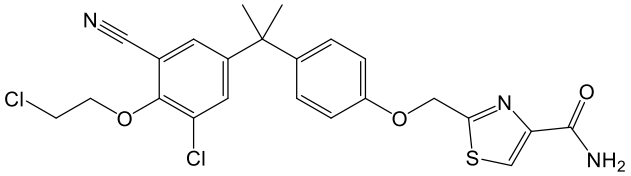
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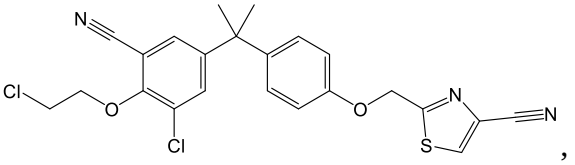
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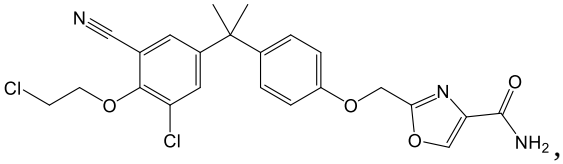
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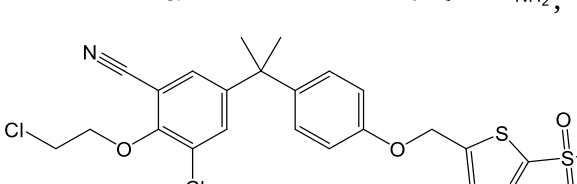
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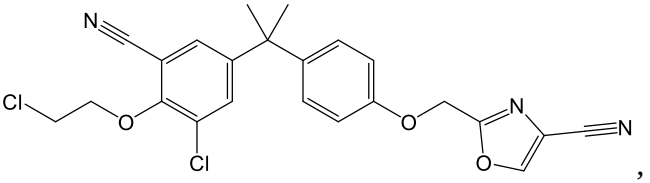
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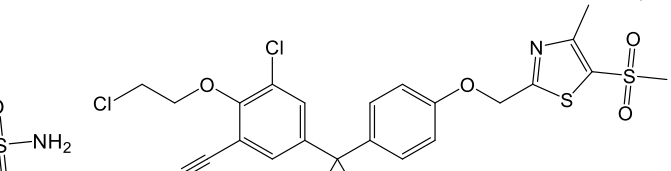
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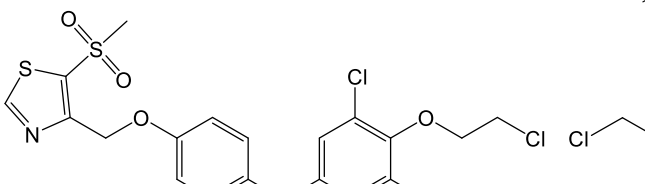
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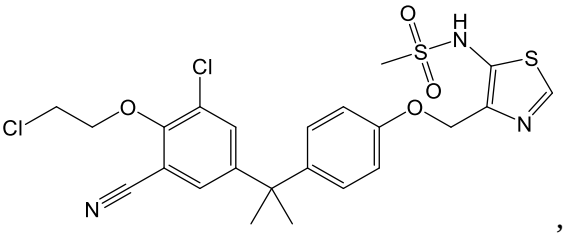
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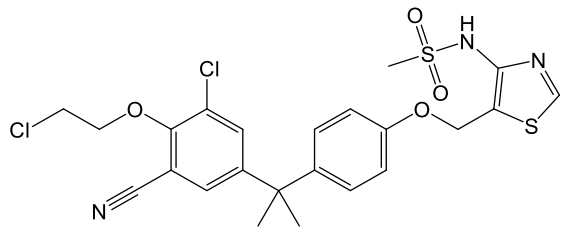
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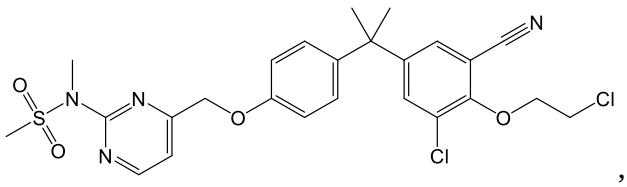
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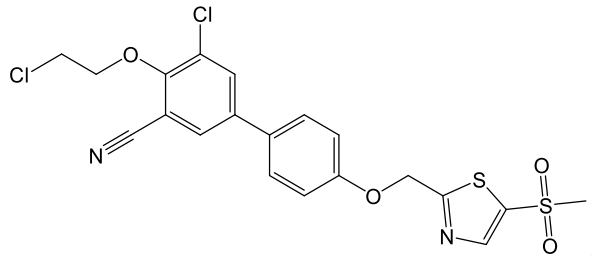
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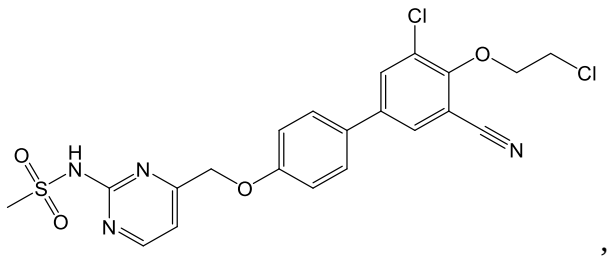
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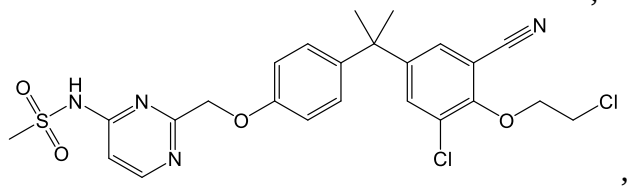
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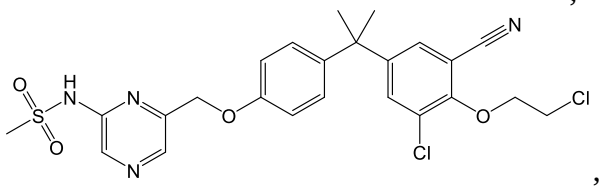
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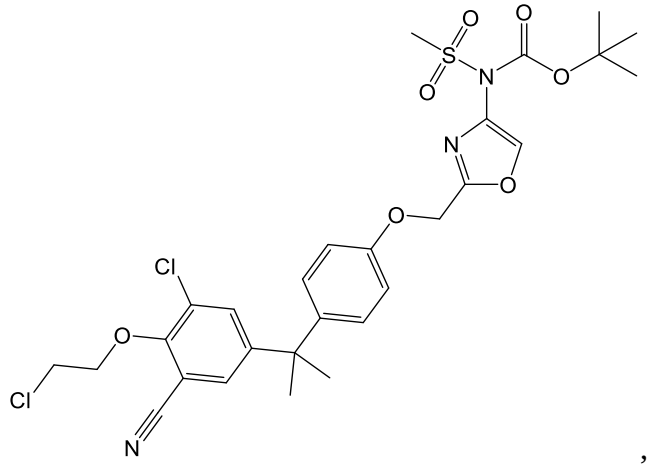
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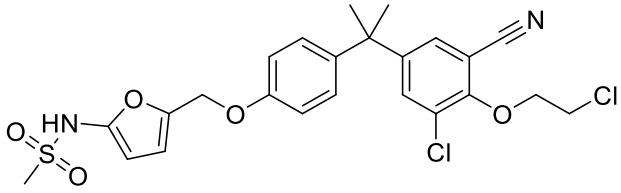
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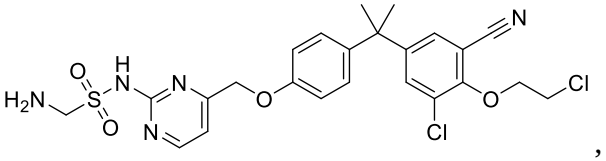
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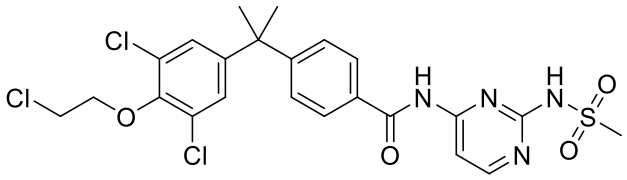
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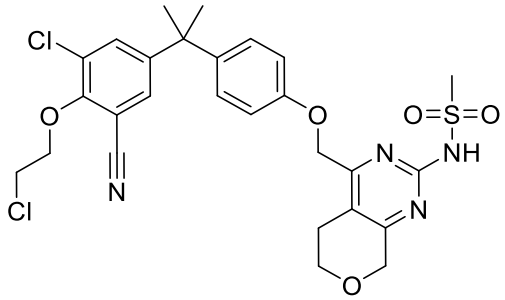
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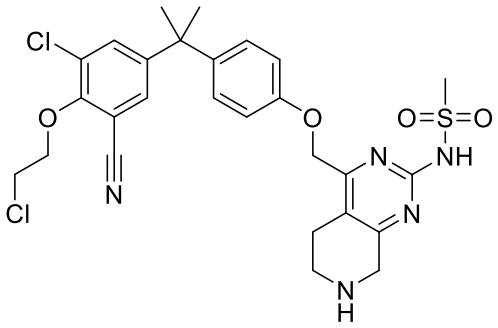
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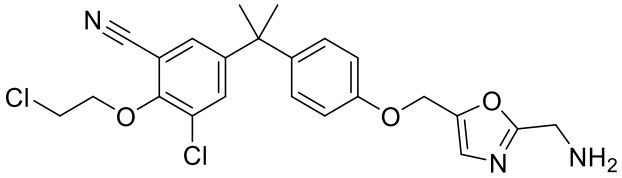
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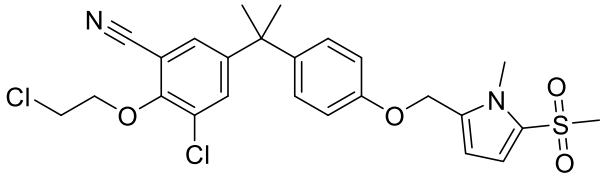
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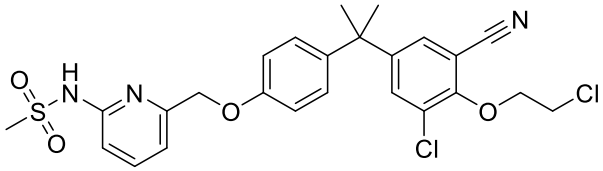
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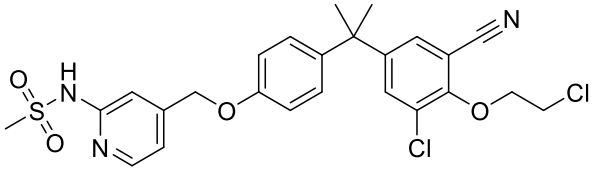
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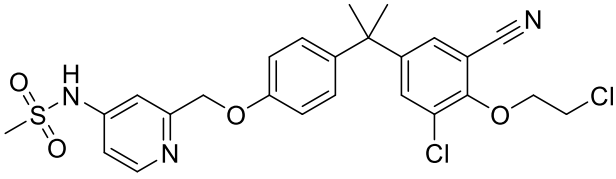
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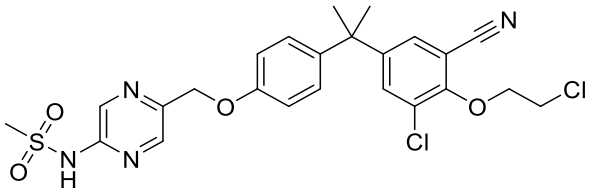
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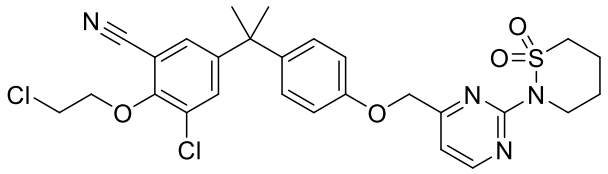
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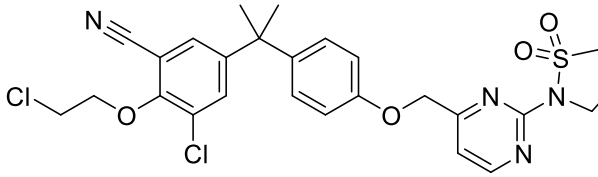
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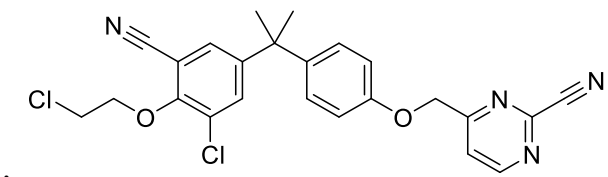
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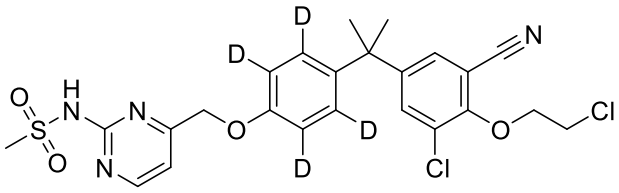
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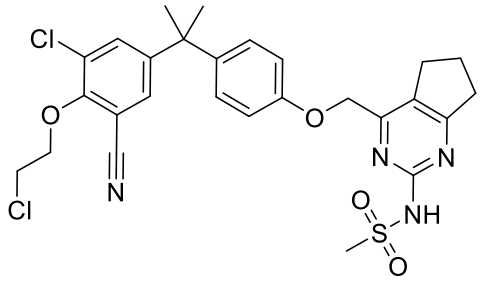
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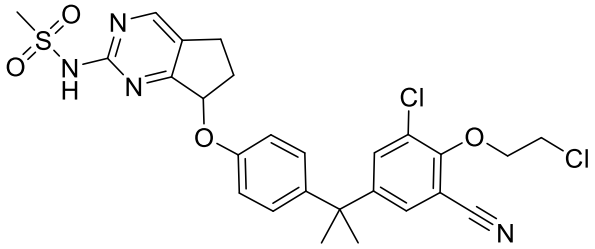
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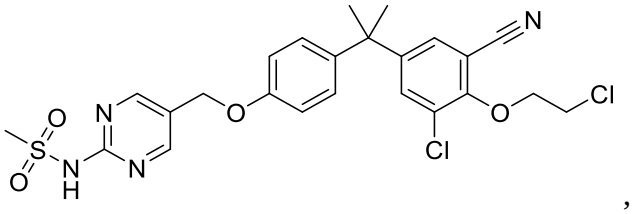
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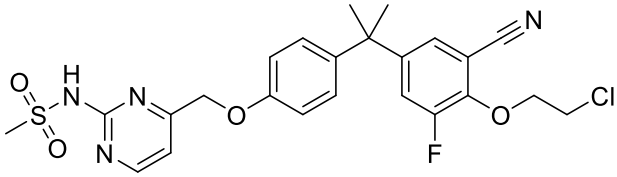
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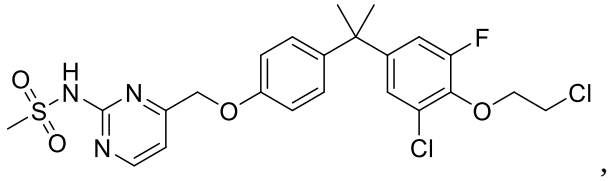
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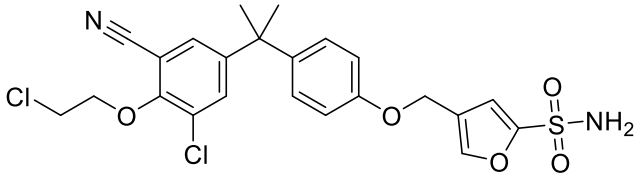
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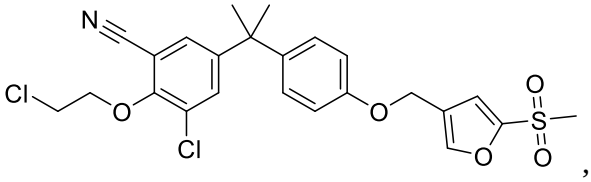
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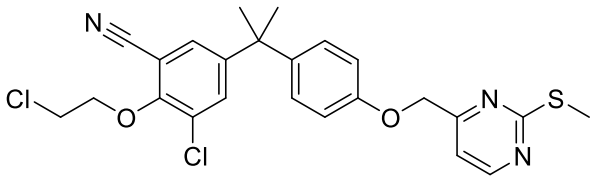
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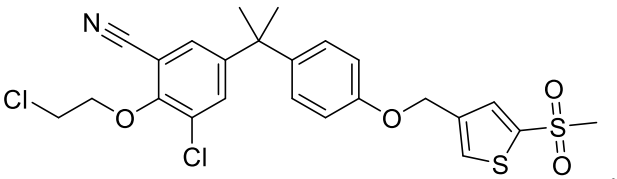
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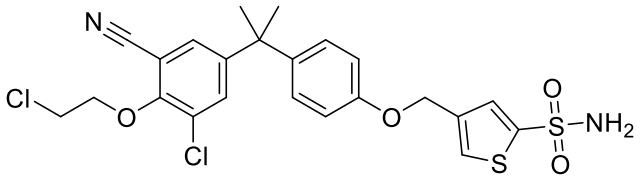
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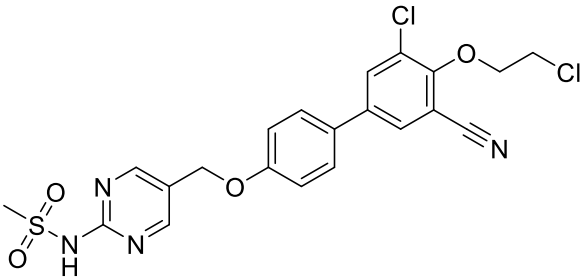
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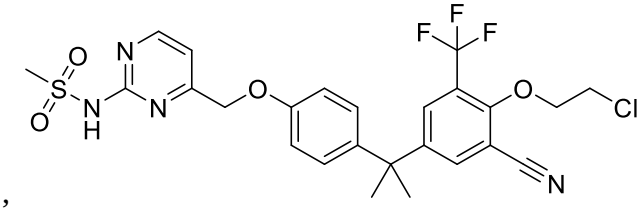
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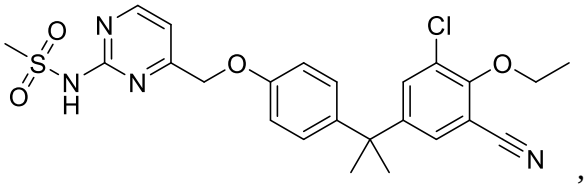
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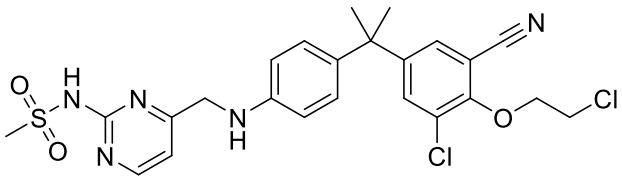
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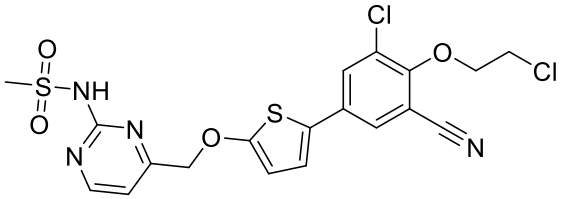
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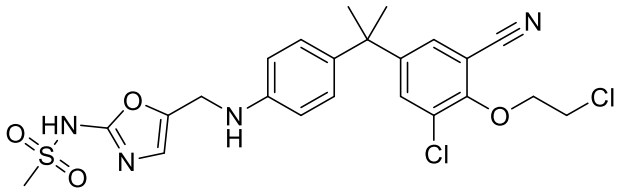
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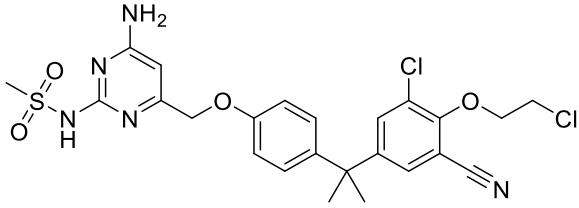
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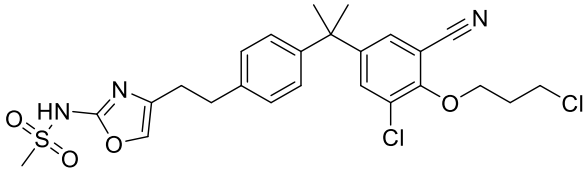
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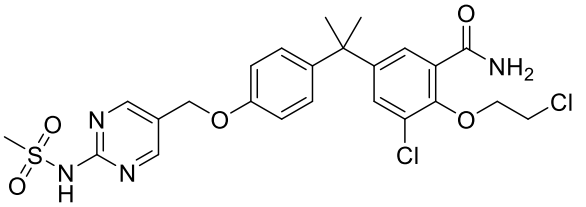
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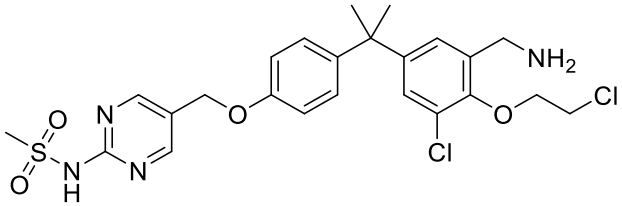
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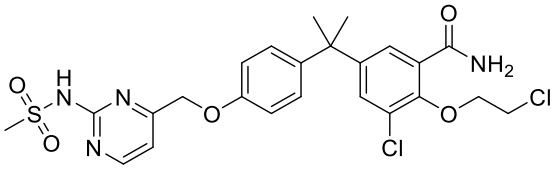
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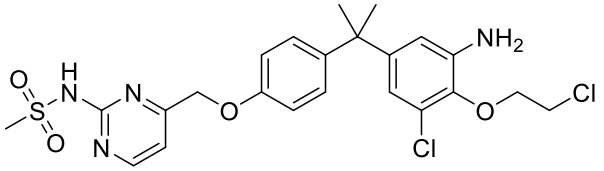
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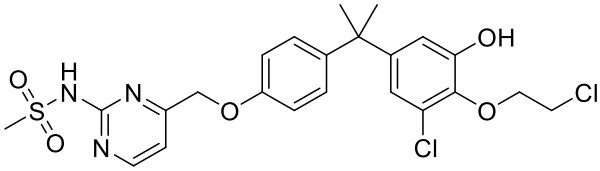
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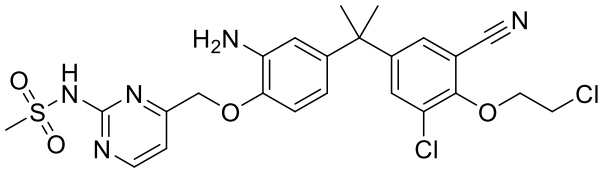
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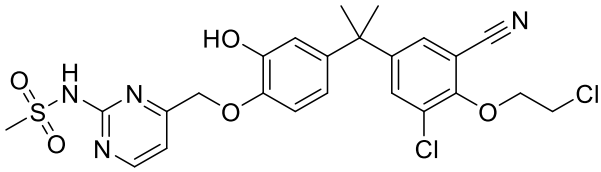
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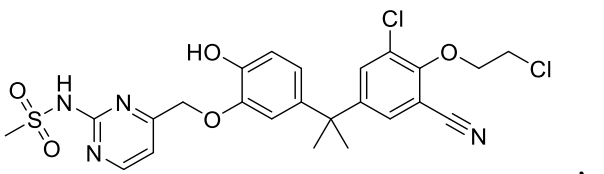
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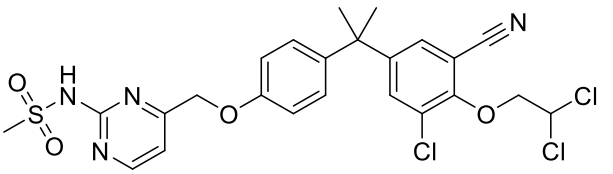
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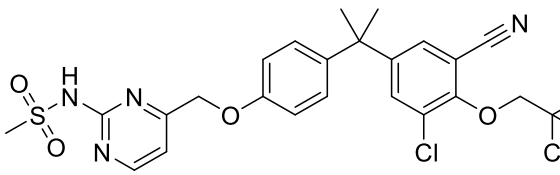
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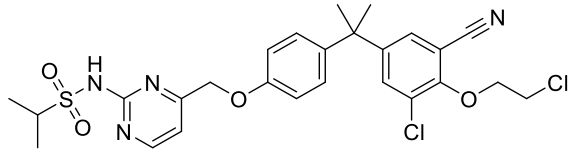
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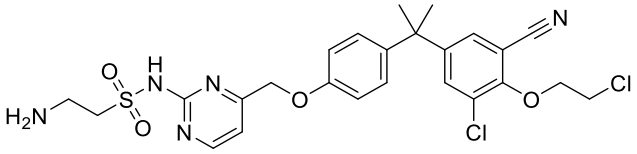
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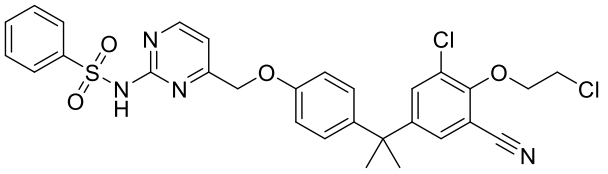
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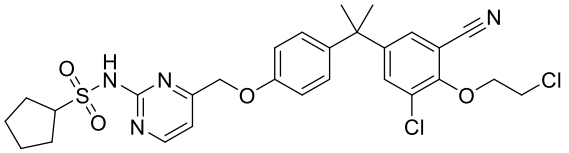
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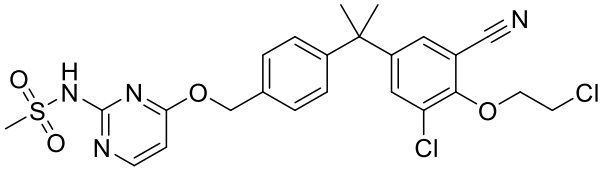
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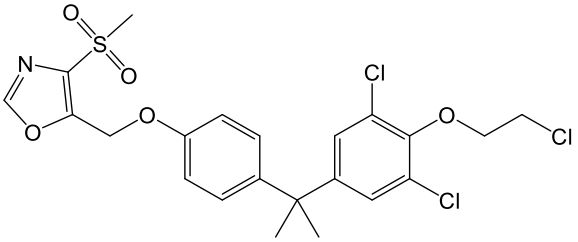
11~~16~~. The compound of claim 10~~15~~, wherein the compound is selected from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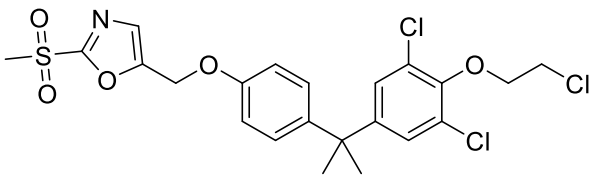
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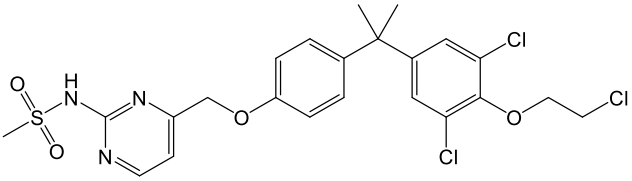
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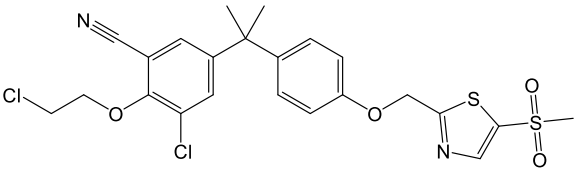
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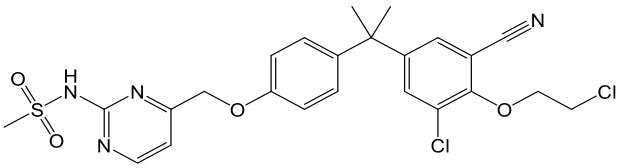
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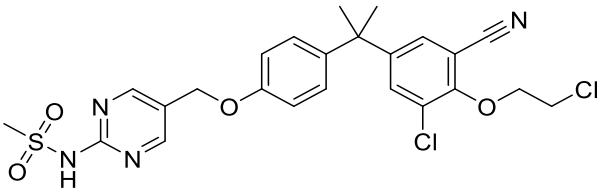
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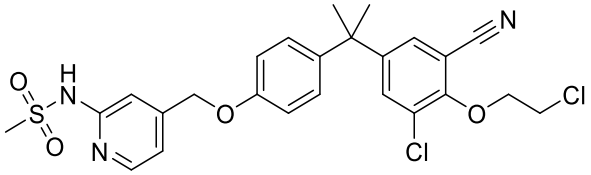
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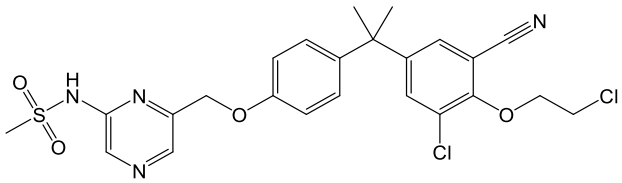
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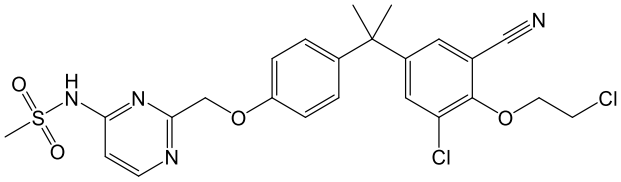
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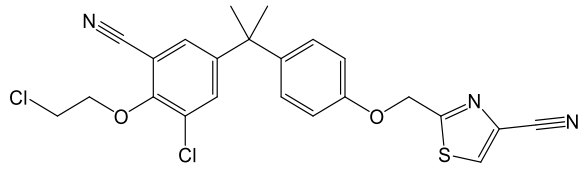
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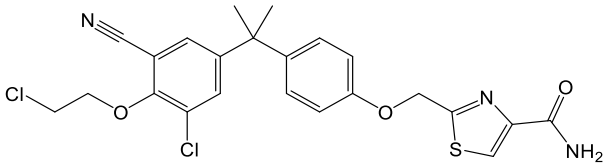
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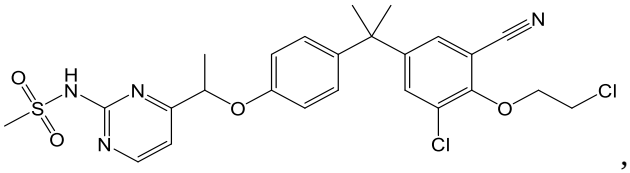
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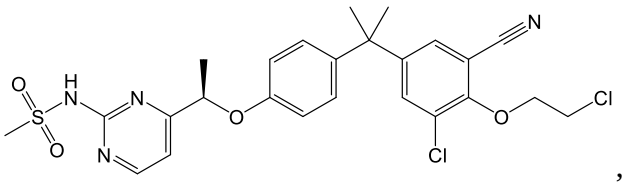
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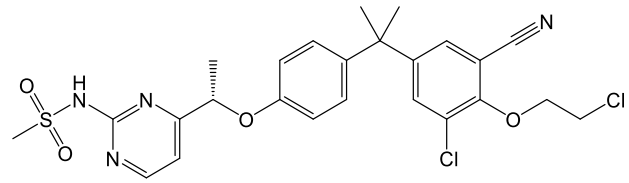
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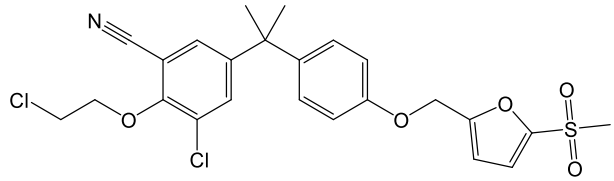
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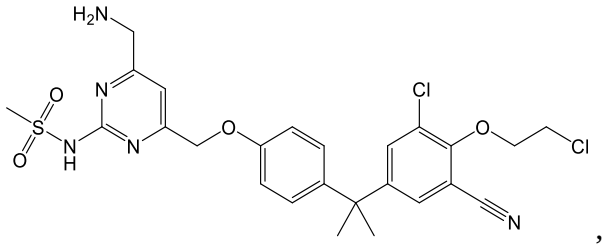
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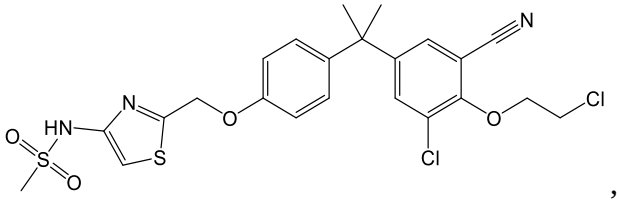
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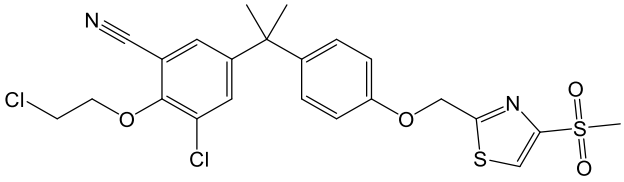
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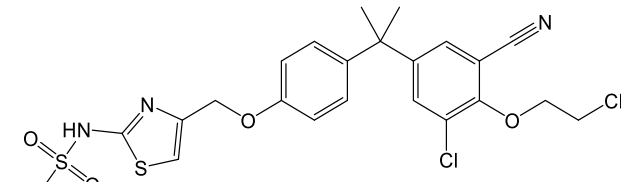
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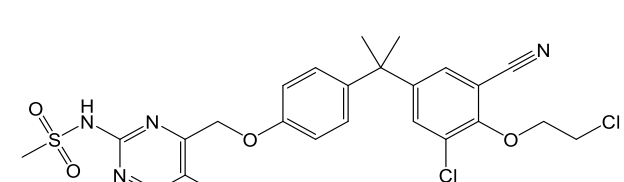
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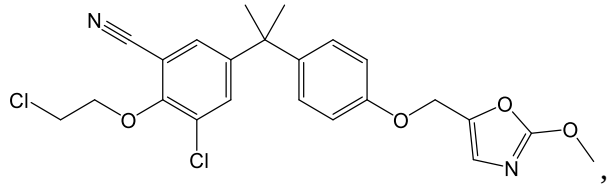
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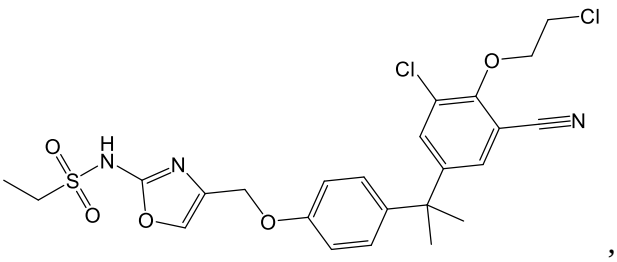
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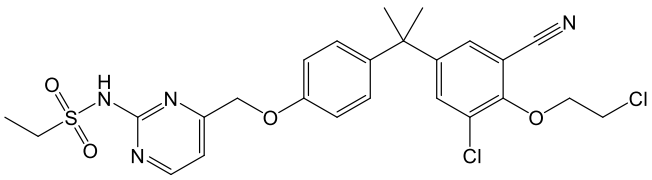


, or a pharmaceutically acceptable salt, tautomer, or stereoisomer ~~or prodrug~~ thereof.

12~~17~~. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

13~~18~~. A pharmaceutical composition comprising a compound of claim 8~~4~~ and a pharmaceutically acceptable carrier.

14~~19~~. A pharmaceutical composition comprising a compound of claim 10 and a pharmaceutically acceptable carrier.

15~~20~~. A pharmaceutical composition comprising a compound of claim 11~~13~~ and a pharmaceutically acceptable carrier.

~~21. A pharmaceutical composition comprising a compound of claim 15 and a pharmaceutically acceptable carrier.~~

~~22. A pharmaceutical composition comprising a compound of claim 16 and a pharmaceutically acceptable carrier.~~

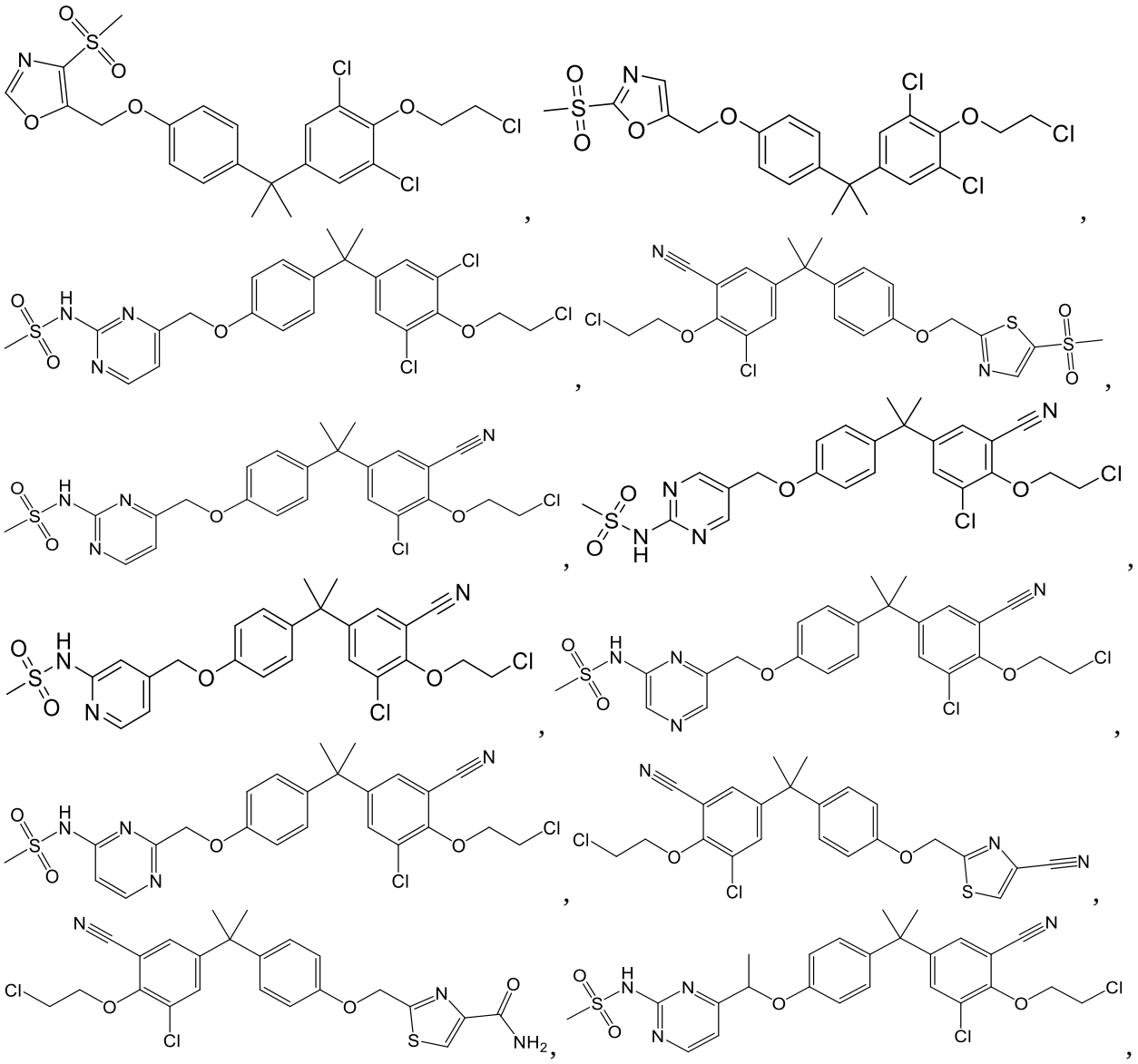
~~23~~16. Use of a compound, pharmaceutically acceptable salt, tautomer, or stereoisomer of the compound of claim 1, in the manufacture of a medicament ~~A method~~ for treating cancer~~, comprising administering the compound, pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug of the compound of claim 1, to a subject in need thereof~~.

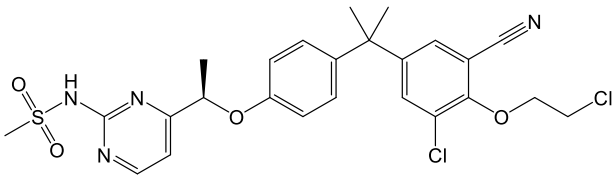
17~~24~~. The ~~method~~ use of claim 16~~23~~, wherein the cancer is prostate cancer.

18~~25~~. The ~~method~~ use of claim 17~~24~~, wherein the prostate cancer is metastatic castration-resistant prostate cancer.

19~~26~~. The use ~~method~~ of claim 18~~25~~, wherein the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant.

20~~27~~. The use ~~method~~ of claim 17~~24~~, wherein the compound is selected from

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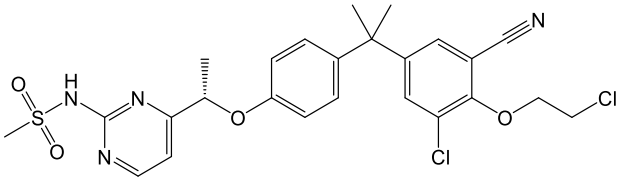
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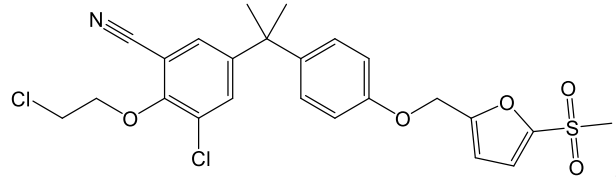
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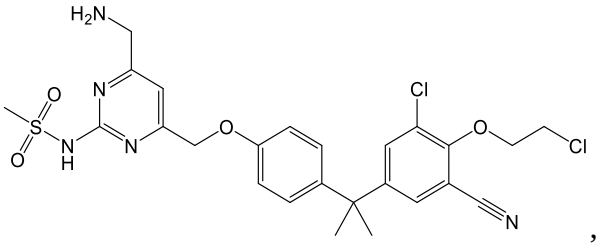
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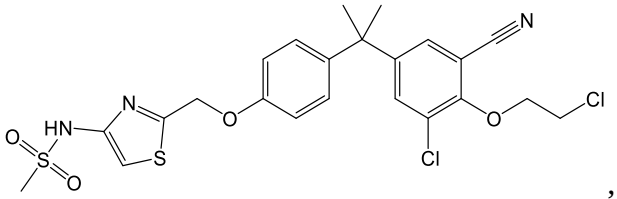
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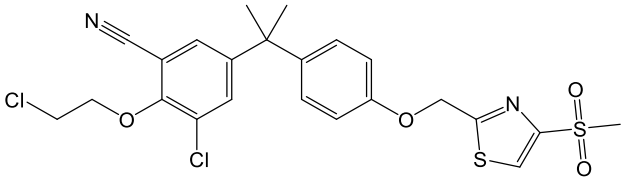
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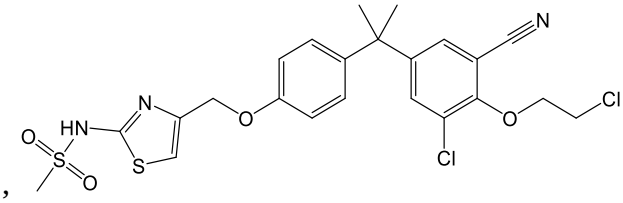
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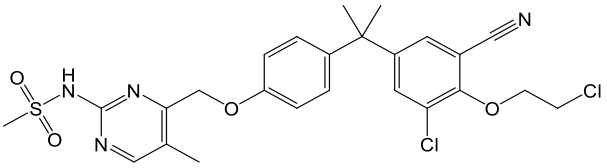
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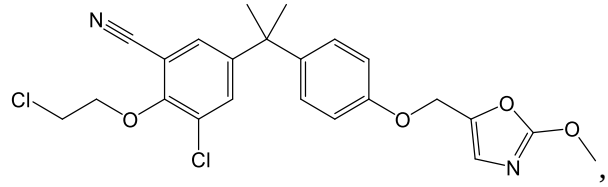
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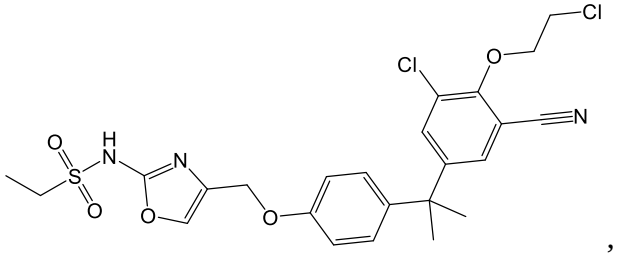
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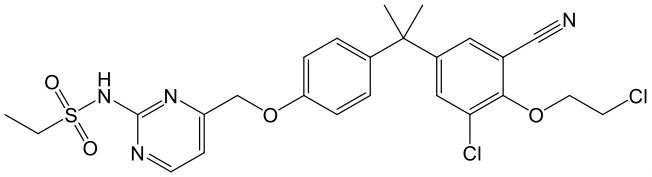
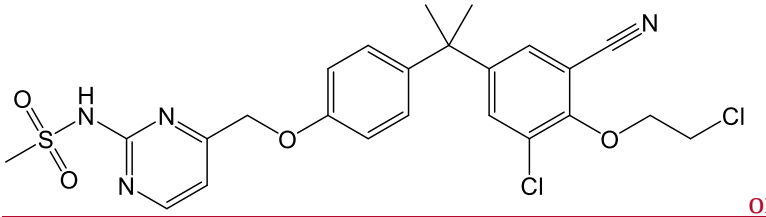

, or a pharmaceutically acceptable salt, tautomer, or stereoisomer ~~or prodrug~~ thereof.

21. A compound having the structure:


or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt of the compound of claim 21, and a pharmaceutically acceptable carrier.

23. Use of a compound or a pharmaceutically acceptable salt of the compound of claim 21, in the manufacture of a medicament for treating prostate cancer.

24. The use of claim 23, wherein the prostate cancer is metastatic castration-resistant prostate cancer.

25. The use of claim 24, wherein the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant.

26. A compound, pharmaceutically acceptable salt, tautomer, or stereoisomer of the compound of claim 1, or a compound or a pharmaceutically acceptable salt of the compound of claim 21, for use in therapy.